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New and Nonofficial Remedies 20 1949

Containing Descriptions of the Articles
Which Stand Accepted by the Council on
Pharmacy and Chemistry of the American
Medical Association on January 1, 1949

Issued Under the Direction and Supervision of
the COUNCIL ON PHARMACY AND CHEMISTRY
of the AMERICAN MEDICAL ASSOCIATION



Philadelphia London Montreal
J. B. LIPPINCOTT COMPANY

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Preface

This book is published under the direction and supervision of the Council on Pharmacy and Chemistry, which is a standing committee appointed by the Board of Trustees of the American Medical Association to consider medicinal and allied preparations offered for adoption.

Since its publication the book is constantly in review by the Council to eliminate preparations which have not lived up to their promise of value, and those which have been official for 20 years. Each year the general articles on the various classifications of drugs are revised and brought them up to date.

Descriptions of such medicinal substances as are accepted by the Council for N. N. R. will be published from time to time in *The Journal* of the American Medical Association. The Council also is responsible for the publication of *Useful Drugs*, the *Epitome of the Pharmacopeia of the United States and National Formulary*, the *Annual Reprints of Council Reports*, as well as articles of interest to the profession from time to time in *The*

The descriptions of accepted articles contained in this book are based in part on the directions of the Council supplied by the author of the rules by which they may be found elsewhere.

Nonproprietary or generic names are presented in the monograph headings in boldface capitals. Protected names, on the other hand appear in boldface capitals and small letters in the heading except where generic names have not been adopted and protected names are serving temporarily as introduction to the monographs in which case the names are presented in boldface capitals followed in parentheses by the name of the manufacturer. Chemical descriptions providing tests and standards for the uniformity of accepted articles have been grouped alphabetically in a section entitled "Tests and Standards."

In line with action taken by the Council during 1943 only the metric system is used in the publications for which the Council is responsible. Adequate conversion tables may be

found in each publication for those who wish to convert other units into metric equivalents.

Criticism of *New and Nonofficial Remedies* is invited with a view to any further improvements of the book.

Acknowledgment is made of the assistance of Diana Korkoneas and Walter Wolman, Ph D.

AUSTIN SMITH, *Editor.*

Contents

	PAGE
Preface	v
Members of the Council on Pharmacy and Chemistry	ix
Consultants During 1948	x
Official Rules of the Council	xiii
Form for Presentation of Articles	xxv
Criteria for the Evaluation of Certain Products	xxviii
Decisions of General Interest	xxxviii
The Council and Official Agencies	xliii
Preparations Specially Exempted from Council Consideration	xliii
Table of Metric Doses with Approximate Apothecary Equivalents	xlviii

SECTION A

CHAPTER

I Agents Used in Allergy	1
II Analgesics	27
III Anesthetics	36
IV Local Anti Infectives	66
V Systemic Anti Infectives	126
VI Antispasmodic Preparations	208
VII Astringents Caustics and Sclerosing Agents	214
VIII Autonomic Drugs	222
IX Cardiovascular Agents	260
X Central Nervous System Stimulants	278
XI Contraceptives	283
XII Diagnostic Aids	292
XIII Diuretics (Mercury Compounds)	316
XIV Gastro intestinal Drugs	333
XV Hematics	347
XVI Hormones and Synthetic Substitutes	358
XVII Agents Used in Metabolic Disorders	410
XVIII Oxytocics	427
XIX Parenteral Solutions	432
XX Pharmaceutical and Therapeutic Aids	434
XXI Sedatives and Hypnotics	440

Consultants During 1948

The following individuals have provided assistance to the Council during 1948 as it considered the addition of new drugs, the omission of other drugs and the revision of statements on actions and uses.

Adams, W. F., M.D.	Chicago, Ill.
Alvarez, Walter, M.D.	Pasadena, Minn.
Alving, Alf., M.D.	Chicago, Ill.
Anderson, H. H., M.D.	Bethel, Calif.
Arnold, Henry, Jr., M.D.	New York, N. Y.
Bell, David C., M.D.	New York, N. Y.
Calder, Leroy A., M.D.	Kansas City, Mo.
Chesed, J. P., M.D.	Green Bay, Wis.
Cook, F. Eubank, M.D.	Philadelphia, Pa.
Cross, E. J., Sc.D.	Columbus, Ohio
Crowson, Robert J., M.D.	St. Louis, Mo.
Cutting, W. C., M.D.	Palo Alto, Calif.
DeGraft, Arthur C., M.D.	New York, N. Y.
DeWess, Lowell, M.D.	Altoona, Pa.
Downing, John G., M.D.	Boston, Mass.
Drugsitt, C. A., M.D.	Chicago, Ill.
Durham, C. I., M.D.	Chicago, Ill.
Eddy, Nathan B., M.D.	Washington, D. C.
Engle, Earle T., Ph.D.	New York, N. Y.
Evans, E. I., M.D.	Richmond, Va.
Feinberg, Samuel M., M.D.	Chicago, Ill.
Freyberg, Richard, M.D.	New York, N. Y.
Gamble, Clarence J., M.D.	Milton, Mass.
Gallen, Ross, M.D.	New York, N. Y.
Gilman, Keith S., M.D.	Durham, N. C.
Gottmacher, Alan F., M.D.	Baltimore, Md.
Hanger, Franklin M., M.D.	New York, N. Y.
Hansen, A. E., M.D.	Galveston, Texas
Hanslik, P. J., M.D.	Palo Alto, Calif.
Hanson, Robert A., M.D.	Baltimore, Md.
Hodges, Paul C., M.D.	Chicago, Ill.
Hunt, Arthur B., M.D.	Rochester, Minn.
Ivy, A. C., M.D.	Chicago, Ill.
Jacoby, Jay J., M.D.	Columbus, Ohio
Jean, P. C., M.D.	Iowa City, Ia.
Katz, Louis N., M.D.	Chicago, Ill.
Keefer, Chester, M.D.	Boston, Mass.
Koch, Sumner L., M.D.	Chicago, Ill.
Lehman, Arnold J., M.D.	Washington, D. C.
Lehr, David, M.D.	New York, N. Y.
Lennox, Win. G., M.D.	Boston, Mass.
Levy, Robert L., M.D.	New York, N. Y.
Livingstone, Huberta M., M.D.	Chicago, Ill.
Lockwood, John S., M.D.	New York, N. Y.
Macbella, Thomas E., M.D.	Philadelphia, Pa.
McLaughlin, Harrison L., M.D.	New York, N. Y.
MacLeod, Colin M., M.D.	New York, N. Y.
Meigs, Joseph V., M.D.	Boston, Mass.

Mudd, Stuart, M D	Philadelphia, Pa
Muehlberger, Clarence, Ph D	Lansing, Mich.
Pakner, Walter L., M D	Chicago, Ill
Pfeiffer, C. C., M D	Urbana, Ill
Raffel, Sidney, M D	Palo Alto, Calif.
Ravdin, I. S., M D	Philadelphia, Pa
Rhoads, Jonathan E., M D	Philadelphia, Pa
Richardson, O. P., M D	Atlanta, Ga
Rittenberg, David, M D	New York, N Y
Rothman, Stephen, M D	Chicago, Ill
Schmitz, Herbert E., M D	Chicago, Ill
Seyers, M. H., M D	Ann Arbor, Mich
Simons, Donald J., M D	New York, N Y
Smith, George Van S., M D	Boston, Mass
Snyder, Franklin, M D	Boston, Mass
Soule, Malcolm H., Sc D	Ann Arbor, Mich
Stuart, Harold C., M D	Boston, Mass
Sulzberger, Marion, M D	New York, N Y
Taylor, Howard C.	New York, N Y
Thorne, George, M D	Boston, Mass
Veldee, Milton V., M D	Washington D C
Wallace, Donald A., Ph.D	Chicago Ill
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Werner, Sidney C., M D	New York, N Y
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Wintrobe M. M., M D	Salt Lake City Utah
Wright, Irving S., M D	New York N Y

The following list contains names of men who assisted the Therapeutic Trials Committee, a standing committee of the Council on Pharmacy and Chemistry, during 1948.

Ackerman, Lauren V., M D	St. Louis, Mo
Adair, Frank E., M D	New York, N Y
Albritton, Errett C., M D	Washington, D C
Allen, Willard, M D	St. Louis, Mo
Austin, J. Harold, M D	Philadelphia, Pa
Badger, George F., M D	Cleveland, Ohio
Beecher, Henry K., M D	Boston, Mass
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Denny, Brown, Derek, M D	Boston, Mass
Dragstedt, C. A., M D	Evanston, Ill
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Muench, Hugo, M D	Boston, Mass
Nathanson, Ira T., M D	Boston, Mass
Pfeiffer, Carl, M D	Chicago, Ill
Platou, R. V., M D	New Orleans, La.
Richardson, R. P., M D	Emory, Ga
Rigler, Leo G., M D	Minneapolis, Minn

Shaw, Edward B., M.D.	San Francisco, Calif.
Sosman, Merrill, M.D.	Detroit, Mich.
Stevenson, Frank E., "	"
Stewart, Fred, M.D.	"
Stout, Arthur Purdy, M.	"
Sutton, Lee E., M.D.	Indianapolis, Ind.
Toomey, John A., M.D.	Cleveland, Ohio
Wall, Joseph S., M.D.	Washington, D. C.
Warren, Shields, M.D.	Boston, Mass.
Wegman, Myron, M.D.	New Orleans, La.
Wilson, James L., M.D.	Ann Arbor, Mich.

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Official Rules of the Council on
Pharmacy and Chemistry

INTRODUCTION

The Council on Pharmacy and Chemistry was created in 1905 as a standing committee appointed by the Board of Trustees of the American Medical Association

Activities of the Council.—The Council publishes an official book dealing with the standards of the medical profession which it has been in that

uses dosage tests and standards of the preparations and articles. The book also contains certain official preparations and other articles including drug substances for manufacturing use for which there are not official standards which the Council is of the opinion should be included for the information of the medical profession.

The activities of the Council also include the preparation of special treatises, articles, status reports and books designed for the practitioner and the medical student; the giving of grants in aid for therapeutic research; the securing of therapeutic trial of promising new preparations and the encouragement of basic research on fundamental therapeutic problems.

Acceptance of Articles for N. N. R.—The principles and policies of the Council concerning the acceptance of a preparation or article for inclusion in *New and Nonofficial Remedies* are briefly expressed in the following rules:

RULES GOVERNING THE ADMISSION OF ARTICLES TO THE BOOK
NEW AND NONOFFICIAL REMEDIES

Rule 1.—COMPOSITION.—The quantitative composition of preparations and articles submitted to the Council or considered by the Council for inclusion in *New and Nonofficial Remedies* must be made known and may be published.

Rule 2.—IDENTIFICATION.—Suitable procedures and criteria for determining the composition or standardization of the submitted preparation or article must be furnished.

Rule 3.—ADVERTISING TO THE PUBLIC.—Preparations and articles promoted to the public for use in the treatment of disease will not be accepted except as specified in the explanatory comments.

Rule 4.—THERAPEUTIC CLAIMS.—When an article is accepted, therapeutic representations by the manufacturers or their agents

must be confined to those given in N. N. R. or accepted by the Council between revisions of N. N. R.

Rule 5.—PROTECTED NAMES—Trademark names for medicinal articles are accepted if the Council deems the use of such protected names not to be harmful to health and if the common or generic names are not unduly subordinated to such trademarks in the labeling and advertising of the products.

Rule 6.—PATENTS AND TRADEMARKS.—If a preparation or product is patented as to process or product or both, the number of such patent or patents must be furnished to the Council. If the name of an article is registered or the label copyrighted, the registration (trademark) name and number and copies of the protected label must be furnished to the Council.

Rule 7.—UNSCIENTIFIC AND USELESS ARTICLES.—A preparation or an article will not be accepted if in the opinion of the Council it will not be in the best interests of rational medicine and the public.

EXPLANATORY COMMENTS ON THE RULES

Rule 1.—COMPOSITION.—The composition of all preparations and articles accepted by the Council for sale must be made known and may be prescribed.

Secrecy Is Out of Place in Medicine.—Intelligent prescribing requires that the physician have access to full information as to the composition of what he prescribes. An article cannot be accepted unless this information is furnished fully and truthfully. Information that is not available for publication at the discretion of the Council is of no service and will not be accepted.

Statement of Composition.—Drugs in interstate commerce must bear on their labeling a statement of composition under the Federal Food, Drug, and Cosmetic Act. Labeling of mixtures that do not come under this Act, such as those sold in intra-state commerce, must contain, if presented to the Council, a statement of the amount of each potent or important ingredient in a given quantity of the mixture. In the case of a definite chemical substance a descriptive (or generic) name satisfactory to the Council is sufficient. In the case of a mixture, the advertiser must submit a request for a statement of composition and propose a statement of composition otherwise.

Vehicles and Preservatives.—The general character of the vehicle and the identity of preservatives or of any other substance, whether added or present as an impurity, must be stated if these can under any circumstances affect the therapeutic action of the article. This does not mean the publication of the details of the working formula.

In the case of preparations for parenteral injection, the identity and amount of preservatives must be declared in the labeling.

practicable, on the carton label or individual package insert, in the event that no preservative is present, the absence must be declared. The term 'preservative' is intended to include all substances used for the purpose of preserving the identity, strength, quality or purity of a preparation. Thus, not only bactericidal or bacteriostatic agents are required to be declared in the labeling but other chemicals, such as stabilizers, anti oxidants and buffers

Benzyl Alcohol—Preparations containing 1 per cent or more of benzyl alcohol must have this ingredient included as part of the name, as benzyl alcohol in such amounts acts as a local anesthetic and constitutes a potent therapeutic agent, for example, solution sodium morrhuate 5% with benzyl alcohol 2%

Chlorobutanol—The Council requires that chlorobutanol be included in the title of those preparations which contain more than 0.5 per cent of chlorobutanol unless the manufacturer can show evidence that the presence of this amount does not have therapeutic as well as antiseptic effect

Nonofficial Drug Constituents—Nonofficial constituents of mixtures must be presented by the manufacturer in the regular way and must be acted on by the Council before the preparations containing them can be accepted

Constituents that are not concerned in the pharmacologic action of the preparation need not be submitted in detail, but their nature and quantity must be disclosed to the Council so that it may be judged that they are inert. The Council may require that they be declared on the labeling by such designations as will make their nature or purpose apparent

Deliberate Misrepresentation—If it appears that a manufacturer has made a deliberately false statement concerning a product he is asked to furnish an explanation, and if this is not satisfactory the product will not be accepted even if the false statement is subsequently corrected or omitted

Testimonials—The foregoing paragraph applies not only to statements made to the Council but also to statements furnished to physicians by the manufacturer or his agents, even when these statements are in the form of testimonials

Inspection of Factories—The Council does not routinely accept invitations to inspect factories, its concern is with the finished products. If such action seems indicated a representative may visit the factory or principal place of business and manufacture to obtain first hand information concerning the manufacturing establishment, the facilities and controls available, the nature of the laboratory and experimental facilities operating in conjunction with the plant, and the scientific personnel and investigative projects

Rule 2—IDENTIFICATION—Suitable procedures and criteria for determining the composition or standardization of the submitted preparation or article must be furnished

The manufacturers of a drug should supply this information, which is necessary to control the quality of an article. For *chemical compounds* this should include tests for identity, amount and purity. In case of *mixtures*, methods for determining the presence and amounts of the *potent ingredients* may suffice. If the tests are described in standard journals or other works, use "physiologically" unless the standard to permit of their control by independent investigators.

Rule 3—ADVERTISING TO THE PUBLIC.—*Preparations and articles promoted to the public for use in the treatment of disease will not be accepted except as specified in the following comments.*

effective treatment, and the spread of infectious diseases when hidden from a responsible physician. All these are involved in the advertising of drugs to the public, with the further dangers of suggesting by description of symptoms to the minds of the people that they are suffering from diseases described, the dangers of the unconscious and innocent formation of a drug habit and the dangers of starting allergic reactions.

Drugs Which May Be Promoted to the Public.—These dangers do not apply in equal degree to all articles, and there are instances in which more good than harm is likely to result from advertisements conveying truthful information to the public, if they do not mislead by undue emphasis or suggestion. The proper promotion of such articles will not preclude their admission to *New and Nonofficial Remedies*; but, in view of the potential dangers to the public, such cases must be carefully weighed and will be confined to the following groups: (a) disinfectants, germicides and antiseptics, provided they are promoted only as prophylactic applications to superficial cuts and abrasions of the skin; (b) laxatives when promoted in such a manner as is not likely to lead to their abuse; (c) antiserums and fractions thereof, vaccines and diagnostic reagents derived from infectious agents; (d) other preparations and articles which in the opinion of the Council could be safely advertised to or used by the public for the relief of symptoms (such as antacids and analgesics). Each group will have to carry adequate and acceptable labeling statements such as "for the relief of minor aches and pains" for analgesics, and "for the treatment of occasional constipation" for laxatives.

Unacceptable Advertising to the Public.—Aside from these specified groups, promotion of articles to the public for the treatment of disease precludes their admission to *New and Nonofficial Remedies*. "Advertising to the public" includes all promotion of the article in newspapers, magazines, radio, films or

any other devices and placards or circulars which may reach the patient

This rule imposes no restriction on the legitimate methods of bringing a remedy to the attention of the profession such as advertising in journals labeling circulars and other printed matter distributed solely to physicians dentists pharmacists and veterinarians provided such promotion does not invite or encourage use by unqualified persons

Advertising the name of a firm as being a reliable one is permissible in any advertising medium

Naming Diseases on Label and Labeling—The naming of diseases and therapeutic indications in the labeling occasionally may be necessary for proper instruction in the use of articles advertised directly to the public and is therefore permissible in the case of the preparations which are accepted for promotion to the public, and where it is required by the Food, Drug and Cosmetic Act.

Permanently Affixed Names—If a prescribed article is dispensed in its original container any permanently affixed device that identifies the article to the consumer constitutes advertising to the public. This includes bottles which have the name of the article blown into the glass and other devices by which the name or initials or other distinctive mark of the article is permanently stamped on the container on the article itself or is on the stoppers or seals. Readily removable labels are not objectionable nor permanently affixed labels on parenteral preparations. The permanent affixing of the firm's initials or name to the trade package is acceptable if such initials or name is not suggestive of the article

Use of Accepted Articles for Advertising Unaccepted Articles—The Council does not countenance the use of an accepted article for advertising other articles which have not been accepted by the Council. The Council therefore objects to the mailing of circulars for accepted and unaccepted articles in one envelope if there is reason to believe that the method of presentation may mislead the reader and if it is not made clear beyond doubt for instance by the initials N N R which of the products have been accepted by the Council and which have not been accepted. This clause does not apply to advertising material circulated exclusively to dealers

When in the opinion of the Council, a firm employs the acceptance of an article in a way that promotes the exploitation of articles that are opposed to the principles of the Council this may be considered as evidence of bad faith which may cancel the acceptance of all preparations of that firm

Acceptance of Article Offered Under Another Name—The Council does not accept an article or continue the acceptance of an article if the same article or an essentially similar one is marketed as a therapeutic agent in the United States by the same firm under another name which has not been recognized.

Advertisements in Foreign Countries—The Council may take into consideration any statements made regarding an article or any method of advertising employed by the manufacturer or his authorized agents or representatives, whether in this country or abroad. No objection will be raised to the use of a statement such as "This substance is accepted by the Council on Pharmacy and Chemistry of the American Medical Association under the name of . . ." when such a statement is used in the promotion of a Council accepted preparation sold outside the United States under another name. The claims in foreign countries should not exceed those accepted by the Council.

The Council does not regard as within its scope the acceptance of articles marketed solely outside the United States.

Films—The Council holds that the term "advertising" includes "advertising literature," films and similar devices for informing the public or profession

Rule 4—THERAPEUTIC CLAIMS.—*When an article is accepted, therapeutic representations by the manufacturers or their agents must be confined to those given in N. N. R. or accepted by the Council between revisions of N. N. R.*

Unwarranted Therapeutic Claims.—Manufacturers or their agents are held responsible for all statements made or quoted in any of their advertising concerning the therapeutic properties of their products. These must be compatible with demonstrable facts.

New Claims—Claims that are not in harmony with already accepted facts or supported by acceptable evidence are not admitted. Therapeutic claims made subsequent to the acceptance of an article must be submitted to the Council for review, if such claims exceed, or substantially modify, those made at the time of acceptance.

Claims for Nontoxicity.—Claims for nontoxicity are admitted only when they do not conflict with known facts. Physicians are cautioned that a claim of lack of toxicity means only that toxic effects have not as yet been recognized with the doses that have been studied. Apparently justified beliefs concerning this point are often ultimately reversed by extended experience. This applies also to claims that drugs are nonirritating

Clinical Evidence.—To be acceptable, the clinical evidence must offer objective data with such citation of authority as will enable the Council to confirm the facts and establish the scientific value of the conclusions. The amount and character of the evidence which is required depend on the inherent probability of the claims; no evidence is needed for a self-evident claim; strong evidence is needed when the claim is contrary to the accepted data of science. The acceptability of evidence is determined mainly by its quality. Multiplication of inaccurate observations does not render them accurate. The evidence must be furnished in sufficient detail to permit judgment as to the care with which it was gathered and the legitimacy of the deduc-

tions. Comparative trials facilitate and are often necessary for such judgment. Observations that are not described with sufficient detail to permit verification are subject to suspicion. The credibility of the data and the justification of the deductions are influenced by the reputation and experience of the investigators as to disinterestedness, technical ability and critical judgment. Anonymous communications and observations gathered without adequate facilities are usually worthless as evidence.

Advertising Copy—In commenting on advertising material the Council endeavors to indicate the type of claims which are acceptable and the nature of objectionable statements. It is not a function of the Council to edit advertising copy word for word but rather to indicate the general type of revision required. The Council holds the firm responsible for compliance with the specifications of the Council's objections and expects the spirit and intent of such objections to be observed in the remainder of the copy not specifically criticized.

Claims advanced in labeling proposed advertisements and other promotional material should not exceed those which the Council permitted at the time that it first gave consideration to the drug concerned or those that the Council may have subsequently found acceptable. Such claims may be found in *New and Nonofficial Remedies*.

As new pieces of advertising copy are prepared they should be made available for Council examination or Council files. If the new material is merely reprinted from material previously accepted by the Council it will not be necessary to have it reviewed by the Council. However if the material presents new claims it must be accompanied by supporting evidence for Council consideration before it is placed in use. Since the claims of the manufacturer are judged largely by their advertising, non-compliance of the manufacturers with the Council's request for copies of the current advertising may be sufficient ground for the rejection of an article.

References to Medical Literature—References to medical literature in advertising for an accepted product should be accompanied by the name of the investigator and year of publication or by full reference to the publication to which reference is made.

Use of Physician's Signature—The use of the personal signature of a physician or the facsimile of such signature on the label or in advertising of products tends to create an exaggerated or misleading impression of therapeutic value through the implication of personal supervision and articles so labeled or advertised are therefore not acceptable.

Rule 5—PROTECTED NAMES—Trademark names for medicinal articles are accepted if the Council deems the use of such protected names not to be harmful to health and if the common or generic names are not unduly subordinated to such trademarks in the labeling and advertising of the products.

Manufacturers are invited to submit proposed names in advance of their registration so that if there is a difference of

opinion as to acceptability, this can be reconciled before the name is trademarked or before a generic name is placed in commerce.

Coining of Name.—The Council recommends that trade names be coined so as to indicate the potent element or constituents.

Advantage of Generic Names.—The Council believes that medical science is promoted by the use of a single ("generic") name for each drug, based on scientific principles and freely available to all. This would avoid much needless tax on memory with its attendant confusion and errors.

Rights to Protected Names.—On the other hand, the Council recognizes that the discoverer of a new remedy has a legal right to a restricted name and that the manufacturer who undertakes the expense of its practical development has a right to some protection and may not feel justified in undertaking the risk if this right is denied.

The Council has therefore conceded acceptance of a protected name to the discoverer or to the firm which first introduced the article. Experience has shown, however, that this restriction to

visible to accept several protected names for the same article, provided there are no reasons which would render this especially objectionable and harmful, provided the names were in use before the product became official (if it is an official drug) and provided the common or generic name is not unduly subordinated to the protected name, in the opinion of the Council. This means that accepted drugs should always be identified by adding the generic or official name when the protected name is used, as, for example, "Luminal, brand of phenobarbital," and "Benzedrine, brand of amphetamine."

Physicians can protect themselves against much confusion by using the generic or official names in speaking or writing of these drugs.

Objectionable Names.—The Council does not accept names

Protected names applied to salts will not be accepted unless suitably coined to apply to the parent therapeutic substance so that they can be qualified to indicate specific salts by addition of the salt designation as a separate and distinct part of the name.

Protected Names for Unoriginal Articles—Protected names will not be recognized for articles which are included in the U S Pharmacopœia or National Formulary or while they are tentatively adopted for such inclusion unless the name was in public use before the drug was admitted to or tentatively adopted for these books. The date of tentative adoption is understood to be that of the first galley proof of the U S P or the N F containing the article concerned.

Protected or coined names that are applied to either official or nonofficial salts or dosage forms of official substances (or simple modifications thereof) are likewise not acceptable except when the firm holds priority rights.

In the marketing of unoriginal articles the legitimate interests of the producer are sufficiently served by identifying such products by appending the name of the manufacturer or agent or by the use of a general brand mark. No objection is made by the Council to the use of such brand marks provided that such mark is not used as a designation for an individual article. Names initials or brand marks of manufacturers or agents when used to denote proprietorship shall not be of such character as to cause any misunderstanding or confusion as to their significance.

Pharmaceutic Preparations and Mixtures—A protected name may be accepted for a pharmaceutic mixture on the ground of originality and if it is a distinct improvement over available preparations to be manufactured ready made by the manufacturer. Rarely involve sufficient originality and it is important that their names should remind the prescriber of their potent ingredients. The Council recognizes however that the development of the practice of pharmacy has been along lines which make it undesirable at times to prepare complicated ointments and suppositories extemporaneously and that there is a tendency for such preparations. This is exceptional for pharmaceutic preparations for prescription by physicians.

Preparations involving a mixture of two or more active primary ingredients that are marketed under protected or coined names which are otherwise unobjectionable are exempted from the requirement that the protected name must be displayed with a common or generic name provided no already existing official or Council adopted generic name suitable for prescribing is applicable to the exact proportions and ingredients of the mixture, and provided all active ingredients are quantitatively declared on the labels for the product. Any coined name should be so framed as to indicate clearly the most potent ingredients. Protected names for such mixtures in which one or more of the active components occurs as a salt are likewise exempted from conformance to the requirement that protected names for salts must include the designation of a given salt as a distinct addition to the name. For the purpose of including acceptable mixtures in New and Nonofficial Remedies but not for labeling of individual products the Council may select a suitable descrip-

tive designation as a title heading under which similar preparations can be appropriately described. Because of variations either in the identity or proportions of the active ingredients in otherwise similar mixtures, the Council recognizes that fully descriptive generic names for prescribing such preparations is not practical and that short protected names offer the safest means of distinctive labeling for these products. The foregoing

The Council may also recognize coined names for pharmaceutical preparations or mixtures that were in actual use before the establishment of the Council and that have been used continuously since that time, and names for mixtures that were named under the reasonably justified bona fide belief that they were chemical compounds, provided such coined names are not otherwise objectionable.

Naming Salts.—Difficulty frequently arises from the application of coined names to salts. For example, a firm introduces the hydrochloride of a synthetic base under the name "Artifi-

the lactate
the name
hydrochloro-
to avoid
for salts

will not be accepted unless such names indicate the components of such salts, thus "Artificialine hydrochloride"; the name "Artificialine," unqualified, is acceptable only for the base.

A similar difficulty may arise when a product is marketed first only as a phar-

wishes to apply

new hypnotic u

facturer elects to market the substance also in powder form, an entirely new name would become necessary and this would cause confusion both to the profession and to the trade. The Council therefore holds that coined names for new substances

accepted only if
the preparation,
at "Aliphal" un-
qualified.

For declaration of benzyl alcohol or chlorobutanol in the name of a product, see comments under Rule I.

Biologic Products.—A biologic product intended for use as a diagnostic reagent, should be designated, e. g. tuberculosis antitoxin. A conclusion in N. N. R. product.

Use of Numerals and Letters—Since the use of numeral or alphabetical designations in connection with drug names tends to take the emphasis away from the name and to displace the name thus leading to confusion the Council will not recognize the name of a drug in which the numeral or letter is an integral part of the name, except in special cases in which the use of a numeral or letter seems desirable because further improvement of the product is anticipated in which case the Council may grant a special exemption from the rule. Under this rule the use of numerals or letters in connection with the name of a product will not be permitted on labels or in advertising unless the numeral or letter is clearly separated from and subordinated to the name by type and if feasible by position. This rule does not apply to price lists and catalogues.

Rule 6—PATENTS AND TRADEMARKS—If a preparation or product is patented as to process or product or both the number of such patent or patents must be furnished to the Council. If the name of an article is registered or the label copyrighted the registration (trademark) name and number and copies of the protected label must be furnished to the Council.

This information is essential to determining the legal status of the article. If it is registered in a foreign country under a different name this information should also be supplied so as to identify the article in the foreign literature.

Rule 7—UNSCIENTIFIC AND USELESS ARTICLES—A preparation or an article will not be accepted if in the opinion of the Council it will not be in the best interests of rational medicine and the public.

Useless drugging is apt to be harmful. This precludes the acceptance of articles which have no definite therapeutic value, of compounds or mixtures with an excessive number of active ingredients or with ingredients that are of no probable assistance to each other and of articles which involve dangers of toxic effects disproportionate to their therapeutic value.

. GENERAL EXPLANATORY COMMENTS

Substances Described in New and Nonofficial Remedies—In the book are described pharmaceutical and drug substances if they have originality or other important qualities which, in the judgment of the Council, entitle them to such place. Official preparations concerning which the Council deems the medical profession not yet fully informed or any other article the inclusion of which is believed to give useful information to the physician.

Previous Noncompliance—The Council judges an article by the facts in evidence at the time of its presentation. Previous noncompliance with the rules (short of intentional fraud) does not prevent at a later date the favorable consideration of an article which is in accord with existing rules.

Reconsideration—Infringements of the rules after acceptance of an article for *New and Nonofficial Remedies* or the discovery

that the Council's information was incorrect, will cause the acceptance to be reconsidered and may be followed by the omission of the article and publication of the reasons for such omission.

Acceptance Not an Indorsement.—The admission of an article does not imply a recommendation for its use. Acceptance simply means that the Council has found no conflict with its rules.

Compliance with Laws.—It may not be superfluous to point out that it is not a function of the Council to determine whether a product complies with the federal, state or municipal laws and regulations. The responsibility for this lies with the manufacturer himself.

Seal of Acceptance.—For articles which are accepted for inclusion in *New and Nonofficial Remedies* the Council permits the use of its official seal of acceptance on the packages of the article and in the advertising for it with the following stipulations: 1. If the seal is used in price lists and catalogues which also feature unaccepted articles, it must be used for accepted articles in such manner that there can be no implication that the seal applies to the unaccepted articles. 2. The following

be used
otes that
nonofficial
Remedies by the Council on Pharmacy and Chemistry of the American Medical Association." Further statements in regard to the seal must be submitted to the Council and be found acceptable before they may be used. 3. The size of the seal on the package shall not be greater than one inch in height or diameter, and in advertising it shall be in proportion to the dimensions of the advertisement so as to afford ready recognition; but undue size, giving greater prominence to the seal than to other important features of the advertisement or detracting from the dignity of the seal in the opinion of the Council, will not be permitted. 4. When for any reason the acceptance of an article is rescinded, the seal must not appear on new labels or in new advertising for such article, and old labels and advertising which feature the seal must not be in circulation, in evidence or before the public longer than six months subsequent to notification of the revocation.

Duration of Acceptance.—Unless otherwise determined at the time of acceptance, articles admitted to *New and Nonofficial Remedies* will be retained during the period they comply with the rules and regulations which are in force. Evidence indicating that the compliance with the rules no longer exists, for instance, with regard to unwarranted therapeutic claims, will be considered the basis for immediately reconsidering acceptance.

All articles are re-examined periodically for compliance with

in which the preparation is held by clinical consultants of the Council

U S P or N F status
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only those mixtures that present some real advantage. The Council endorses the principle that prescriptions should be written on the basis of the therapeutic effects of the individual ingredients. It recognizes, however, that at times it may be advantageous to prescribe more than one ingredient in the same product. A further explanation may be found under explanatory comments on Rule 5.

Diagnostic Reagents—P
 which are not used in or
 for inclusion in N N R
 Council may determine the status of such products individually

PRESENTATION OF ARTICLES FOR N N R

ELIGIBILITY FOR N N R.

Before submitting any article for inclusion in N N R, a careful study of the Official Rules and of N N R should be made to determine its eligibility for acceptance by the Council. Articles of questionable eligibility may have their status determined prior to formal presentation on request of the manufacturer. Such preliminary requests directed to the Council office may avoid waste of time for all concerned.

New drugs, not yet released for commercial distribution by the Food & Drug Administration, will not be accepted until passed by that agency unless it seems evident that the product will be placed in interstate commerce. The Council restricts acceptance to articles that are available on the market or soon to be placed thereon and to articles that are marketed in the United States.

1 Articles re-
 jected by the to
 overcome pre in-
 clusion in N orts
 of the Council on articles previously rejected or on which un-
 favorable action has been taken will be found in the Biblio-
 graphic Index of N N R.

2 Articles that have had official (U S P or N F) status for more than 20 years (except products licensable under the Serums, Virus and Vaccine Act, including arsenicals for syphilis, which are admissible) or have been specifically exempted from consideration by previous action of the Council, are likewise in

general ineligible for N. N. R. (Report of the Council: Preparations Exempt from Council Consideration, J. A. M. A. 129: 1017 [Dec. 8] 1945).

3. Articles advertised to the public without adequate directions for use or against abuse or that are not considered safe for use by the general population without medical supervision are ineligible for inclusion in N. N. R. Thus far the Council has classified as safe for public use (a) antiseptics for prophylactic application to minor injuries of the skin, (b) laxatives not prone to abuse, (c) antacids and analgesics that can be safely used for the temporary relief of symptoms, (d) pediculicides which are considered safe for self-application.

4. Articles of nonmedical significance or that are not intended for the diagnosis, prevention or treatment of disease are not eligible for N. N. R. Thus, articles not used in or on the human body, or used outside the body for purposes that are not directly or indirectly of medical significance, would not come within the purview of the Council.

5. Instruments or devices per se that do not directly involve consideration of some medicinal or pharmaceutical substance are also outside the purview of the Council.

Method of Presentation.—The procedure in submitting an article to the Council consists in forwarding to the Secretary: A complete description of the product (dated and signed) in duplicate, in accordance with the form outlined in subsequent paragraphs; three trade packages of each dosage form of the product to be considered (not to include more than one quantity package of identical lots of the same item), one sample of each active ingredient contained in the product; 22 copies each of all labels (container, package, carton), package enclosures (leaflet or circular) for each submitted dosage form and of each piece of advertising for the product that is distributed or intended for distribution.

In the event no promotional material other than labeling is employed, a statement to that effect should be made, with the understanding and agreement that should advertising or promotional material subsequently be proposed for distribution, copies of such material will be submitted to the Council before it is placed in distribution. Advertising for submitted articles that mentions other products not submitted or not already approved by the Council for inclusion in N. N. R. cannot be approved for distribution unless the advertising is revised to eliminate the unsolicited items.

Consideration is expedited if the labels are submitted on separate sheets so that 22 separate sets of labels will be available for examination. In the case of new drugs or of well known drugs in which new therapeutic claims are advanced, the original submission should be supplemented by 22 copies of written summaries (or abstracts) of all available experimental and clinical studies including references to the published and unpublished or other sources from which data is derived. The

dence is not required so long as the claims do not go beyond the statements made in that publication. When the article is simply a dosage form of a brand of the product already accepted, only that information essential to supplement the original presentation of the article to afford a clear description of the composition and purpose of the new dosage form is required, in addition to the necessary specimens and copies of the labeling and any new advertising. When two or more dosage forms of the same product are submitted together, the information may frequently be combined in the same outline when that is feasible. The inclusion of unacceptable dosage forms (or mention of them in the advertising) in a presentation submitted for otherwise acceptable items of the same product frequently causes delay in acceptance of the recognized dosage forms. Separate outlines for dosage forms involving special vehicles or bases may avoid the confusion that sometimes arises in this connection. The Council has restricted acceptance of certain products to dosage forms of specific size or concentration that is indicated either in the Official Rules or in N N R under the general statements for the class of articles affected.

OUTLINE OF DESCRIPTION

1 *Name of Product*—The protected (trademark) or coined name if any should be supplied; otherwise the common name used to designate the product may be given. The common name should, when applicable, conform to the official (U S P or N F) designation or the nonproprietary (generic) name adopted by the Council. Protected names should comply with all stipulations of rule 5 concerning acceptable nomenclature and should be followed at this point of the outline with a brief explanatory statement of the significance and reason for choice together with the date the name was first used publicly to designate the product. (The Council does not recognize protected names that were not in public use prior to admission of the article to official status in the U S P or N F or tentative adoption for inclusion in these books.) The name (protected or otherwise) should be reasonably descriptive if possible of the principal active ingredient; should include the designation of the

that may be produced a prominent, though secondary therapeutic effect (intended or otherwise) are required to be declared as part of the name for the product, e. g. Solution Sodium Morrhuate 5 per cent with Benzyl Alcohol 1 per cent. Care should be taken that

- (m) Are representative samples of each lot of the drug examined by any other laboratory (government or private) prior to distribution? If so, by whom?

6. *Tests*.—If the article is a chemical substance, there must be

7. *Pharmacologic Action*.—General information is necessary

supplement to the information given under this heading.

8. *Therapeutic Indications*.—A brief statement of the conditions for which the article is claimed to be indicated should be included. These should correspond to the actions and uses given in N. N. R. when applicable. If the article is claimed to be used for any other purpose, this should be outlined under this heading. In general, this should include a summary of the various conditions treated, the number and type of cases treated, the results obtained, and the evidence given in the preceding sections. All claims must be supported by evidence given in the preceding sections. When extensive, the detailed reports may be submitted in duplicate and 22 copies of a suitable comprehensive and unbiased summary or abstract

tation, accompanied with 22 copies of each, and a suitable reproduction of the evidence. When extensive, the detailed reports may be submitted in duplicate and 22 copies of a suitable comprehensive and unbiased summary or abstract

furnished for the Council Care should be taken to see that the therapeutic claims that appear in the advertising for the product correspond to the indications and evidence given in this presentation.

9 *Dosage*.—When applicable the dosage and method of administration recommended should correspond to the one specified in N N R. When the product is a new dosage form of an article otherwise described in N N R the details of dosage and administration for the proposed product should be given together with any necessary precautions peculiar to its mode of application. Similar care should be taken to supply all essential dosage information for a new drug.

10 *How Supplied*.—A list should be given of all dosage forms sizes and package forms of the article that are intended for consideration by the Council and that are described in the foregoing outline. A statement should also be included to indicate whether or not the active ingredient is marketed in bulk.

11 *Manufacturer*.—The name of the firm that is responsible for the finished article as labeled and the names of the manufacturers of all ingredients contained in the article must be stated.

12 *Patents and Trademarks*.—When pertinent the number of the U S patent and number of the patent in the country of origin is necessary. If the article bears a registered trademark, its number and if registered in foreign countries the name or names under which it is so registered is also required.

If the product is one of which no brand has been previously admitted to *New and Nonofficial Remedies* the manufacturer or responsible agent must present protocols of laboratory and clinical evaluations (toxicity pharmacology therapeutics deterioration, etc.) Such protocols should include not only evidence collected by the firm in its own investigations, but references to published papers if available. Twenty two copies of this material must be provided so that each member of the Council can examine at first hand all submitted evidence. If the material is so exhaustive that 22 copies are impracticable the firm may submit only two copies of all evidence and 20 copies of an unbiased abstract of the evidence. The abstract in fact the entire presentation may be submitted in mimeographed form.

Firms submitting for the first time an article eligible for inclusion in N N R are required to supply with the presentation 22 copies of the catalog price list or other suitable tabulation of all products sold by the firms for human medicinal use.

The following information is requested in duplicate

(a) A statement of the laboratory and control personnel of the firm and their qualifications

(b) A general statement of the firm's policies with respect to its scientific aims and methods of marketing drugs either for the public or for the profession. This should include present practices as well as any future plans

clinical tests should not be conducted on patients who are employed in plants which have a gainful interest in the fungicide being tested.

(g) Local Irritant Effect of Fungicide This should be substantially nil, considering the number of fairly effective therapeutic agents now existent which are free from irritant effects. Certainly, the development of any reactions that are at all severe should at once condemn the agent.

(h) Sensitization to the Fungicide This factor enters into and is routinely inquired for in tests of local applications in . . . will largely take care . . . idal value, where the . . . ical course of events . . . r the eighth day of . . . do appear, a special . . .

(i) Toxic Systemic Effects These should not play a role of importance in the treatment of dermatophytosis. Animal tests . . .

(1911), Vol. 13, 1942, page . . .
in this connection

(j) Readings of Results of Treatment These should be made without any knowledge of the identity of the patient or of the treatment that has been employed, an assistant should have removed if possible, any traces of telltale fungicide that may remain. Only in this way can the factor of bias be completely removed and a fair, impartial evaluation secured. If at all possible, the readings should be made by a disinterested person.

(k) Mycologic Checks on Therapeutic Results These will have value only of a kind supplementary to the clinical opinions because of the increased difficulty in laboratory demonstration of fungi in treated lesions. At the conclusion of therapy they should be made on the "cured" and "nearly cured" patients and again . . .

portance

cases available for subsequent statistical purposes and illustrates once again the necessity for numerous patients to begin with.

be conducive to accuracy if the physician has an assistant who will independently grade the results, the final grading being decided in consultation on the spot.

3. *Toxicity Tests.*—These should be performed depending on the individual circumstances surrounding the chemical concerned. Where there is a hazard the Bureau of Ships circular entitled "Disinfectant, Germicide and Fungicide," page 4, paragraph F-2d may be followed. Ten healthy adult albino rats weighing between 150 and 250 Gm. should be employed, none pregnant. They should be fed as usual. Three-tenths cc. of the fungicide (standard strength) per kilogram of body weight should be slowly inserted obliquely into the peritoneal cavity. The animal should then be given the usual food and water and observed for untoward effects for 72 hours.

CHEMICAL CONTRACEPTIVE AGENTS.—For guidance in reviewing contraceptive products, the Council on Pharmacy and Chemistry has proposed the following criteria:

1. The use of the word "contraceptive" need not be limited to materials which will prevent conception on every occasion of use.

2. Evidence shall be furnished that use of the material decreases the incidence of pregnancy. This evidence may be secured in connection with occlusive devices unless the manufacturer's advertising is directed chiefly toward the use of the jelly or cream without such devices. It is desirable that each case reported should be observed for at least 12 months, and that the minimum of 75 patient-years of experience should be reported. (Thus 50 patients for 18 months or 25 patients each followed for 3 years would be the equivalent of 75 patients for 12 months.) If cases are excluded from the series on the basis of their being irregular users, the number excluded and the nature of the evidence justifying their exclusion should be stated.

3. Evidence shall be submitted that 100 or more couples have used the material on six or more occasions without irritation or injury.

4. Evidence is desirable that 12 or more women have received vaginal applications of the recommended dosage on 21 successive days without subjective irritation or injury and without evidence of physical damage shown on speculum examination by a physician with special experience in this field. Thus, inspection of the vagina at least once a week should be done as a protection to the patient in case the jelly proves to be irritating.

5. The quantitative formula from which the contraceptive mixture is prepared shall seem to the Advisory Committee to be safe and, presumably, effective.

6. The consistency shall be satisfactory to the committee. It shall not show separation into more liquid and more solid portions visible to the naked eye.

7. Evidence shall be submitted that the consistency is not substantially changed after storage for 12 months at 27° C.

8. The consistency shall be reasonably uniform from batch to batch.

10. The use of jellies or creams suggested by the manufacturer need not be limited to use in conjunction with an occlusive device.

11. If a syringe applicator or nozzle is furnished for use in connection with the jelly or cream it shall be sufficiently translucent to permit the detection of air which might lead to inadequate dosage.

12. If a perfume is used, a quantitative statement of ingredients is required.

DECISIONS OF GENERAL INTEREST

In order to aid manufacturers and distributors of medicinal articles which conform to the requirements of the Council's rules, certain statements which have been adopted by the Council are herewith presented.

The Use of Numbers and Letters in Names

Some time ago the Council adopted the following statement expressing its attitude and requirements with regard to the use of numeral and alphabetical designations in the names of pharmaceutical products:

"The use of numbers and letters in the names of pharmaceutical products should be such as to avoid any confusion with the name of the product, and to avoid any suggestion of a substitute for the name of the product."

numeral or letter is an integral part of the name, except in special cases where the use of a numeral or letter seems desirable because further improvement of the product is anticipated, in which case the Council may grant a special exemption from the rule. Under this rule the use of numerals or letters in connection with the name of a product will not be permitted on labels or in advertising, unless the numeral or letter is clearly separated from and subordinated to the name by type and if feasible by position. This rule does not apply to price lists and catalogs."

The rule has been interpreted to apply also to alphabetical and numeral combinations which are sometimes used as trademarks. Such devices, when used as an integral part of a name or in a manner which would tend to promote their use as a substitute for a proper name, are held to be objectionable.

The guiding principle in the enforcement of this rule is fairly simple. The Council wishes to avoid any disposition of numbers that would tend to make them a part of the name or a substitute for it, in the minds of the prescriber or the public. It countenances their use only for the convenience of the wholesaler.

To aid manufacturers and distributors in the preparation of labels which meet the requirements of this rule, the Council offers the following examples of acceptable and unacceptable number set-ups on labels:

Acceptable

ELIXIR BROMIDES
COMPOUND
No. 42

100 cc. List No. 88

SYRUP
EPHEDRINE COMPOUND

Unacceptable

ELIXIR No. 42 BROMIDES
COMPOUND

SYRUP
EPHEDRINE COMPOUND
No. 88

(The typography of the numbers in the "acceptable" labels should be subordinate to that of the name itself.)

* These examples do not cover all types of labels but they should serve to give some idea of what the Council is attempting to accomplish in the way of compliance with its rule prohibiting the use of numbers as integral parts of names.

These principles apply also to collateral advertising. No objection is made to the following examples of acceptable collateral advertising.

Spelling of Basic Products Having an "Amine" Group

The Council has expressed its opinion that the use of the ending "ine" in the names of basic products is not acceptable. It is recommended that the ending "ine" be replaced by "ine" in the names of basic products.

whereas the ending "ine" would indicate that the compound is of a basic character. This style of nomenclature is not acceptable.

required adoption of this style of nomenclature for new products submitted to it, and, for the sake of uniformity it urges adoption of the final "e," where needed, for old products as well. The Council asked all firms to cooperate in adopting this style of nomenclature and revise the names of their products which are basic and contain an "amine" group to include the final "e"

Advertising Brochures

The Council will continue to examine reasonably brief advertising brochures in the light of nomenclature rules. The Council

Uniform Spelling of "Ampul" and "Ampuls"

The Council voted to adopt the spelling "Ampuls" for the form of container for the names of drugs. It is requested that an effort be made to obtain conformity with the preferred spelling but failure to effect the change will not be held as a bar to Council acceptance of a drug.

Enteric Coated Forms of Diethylstilbestrol and Nidital

The Council has received evidence is submitted to show that they possess advantageous properties. There appears to be no evidence that enteric coated forms are superior to the plain dosage forms either from the standpoint of stability, therapeutic efficiency, or incidence of toxicity symptoms.

Mineral Waters

The Council considers that artificial mineral waters are non-essential modifications of natural waters, and that natural

these preparations.

Nasal Inhalant Preparations Containing Petrolatum

For several years brands of nasal inhalant preparations marketed in oily or ointment vehicles, consisting wholly or in part of petrolatum (principally liquid petrolatum) were included in *New and Nonofficial Remedies*. The Council reviewed the status of such preparations and is of the opinion that the repeated use of nasal inhalant preparations containing a vehicle of liquid petrolatum may lead to undesirable effects and is accordingly

brands of inhalant n
cause of the danger
use and the fact tha
tions are available

10 Per Cent Solutions of Sodium Morrhuate Not Acceptable

For some time the Council recognized the use of solutions of sodium morrhuate as a sclerosing agent for the injection treatment of varicose veins, and both 5 per cent and 10 per cent

solutions in combination with a local anesthetic were accepted for inclusion in *New and Nonofficial Remedies*. After due con-

treatment of varicose veins

The Council authorized a revision of N N R to include a recommendation for the use of a preliminary test dose as a precaution against untoward reactions with 5 per cent solutions

Avoidance of "Split Titles" on Labels

Several instances have arisen in which the Council has been asked to give an opinion concerning the formulation of titles on labels. The following forms are submitted as examples

SYNTHETIN
(Reg. U S Patent Office)
HYDROCHLORIDE

SYNTHETIN
Brand of—(generic name)
HYDROCHLORIDE

The Council ruled that the splitting of names was objectionable, in that it might lead to confusion on the part of physicians and pharmacists and should therefore be avoided. It was recommended that the labels given above be revised as follows

SYNTHETIN HYDROCHLORIDE
(Synthetin is registered in the U S Patent Office)

SYNTHETIN* HYDROCHLORIDE
*BRAND OF—(GENERIC OR CHEMICAL NAME)

Therapeutic Agents Derived from Animal Sources for
Parenteral Use

The Council has considered the reasonable possibility that the

source of animal products be declared on the label for accepted brands of noncrystalline products for parenteral injection and

Variations in Labeled Content of Accepted Preparations

Preparations varying beyond 5 per cent plus or minus of labeled content will be accepted only if such variation may be especially justified.

Definition of "Label" and "Labeling"

The Council voted to adopt the definition of the Federal Food, drug and Cosmetic Act of "label" and "labeling," which is given as follows:

wrappers accompanying such article.

The Council and Official Agencies

The Relation of the Council to Other Bodies and to Governmental Agencies Regulating Drug Products and Their Advertising

descriptions of their organizations and duties are given

The Food and Drug Administration This agency is part of the Federal Security Agency and is charged with the enforcement of the Federal Food, Drug and Cosmetic Act, the Caustic Poison Act and several other statutes. The Food and Drug Administration is directed by the Commissioner of Foods and

special laboratories are located in Washington

The Federal Food, Drug and Cosmetic Act regulates the labeling of drug products but its authority does not extend to advertising. Seizure of offending goods, or criminal prosecution of responsible firms or persons in federal courts are among the methods used to enforce the provisions of the Act. In addition, repeated violations may be enjoined by the courts.

Violations may consist of both Adulteration and Misbranding of an article whereas labeling refers to the labeling of the article.

Labeling refers not only to the labels on the immediate con-

The Food, Drug and Cosmetic Act prohibits certain things from appearing in the labeling i.e., any statement which is false or misleading. It also requires certain things to appear in the

labeling, i.e., a statement of the quantity of contents, the name and address of the manufacturer or distributor, the name and

deceptively packaged. New drugs may not be introduced into the market unless they have been permitted to show by adequate use under the con-

Certain drugs, namely, insulin, penicillin, and streptomycin, are subject to special control. Samples of each batch of these drugs are examined by the Food and Drug Administration for compliance with standards set forth in regulations issued by the

The Federal Trade Commission: The Federal Trade Commission is an independent agency of the Federal Government directly responsible to the President. The Commission administers several laws, the principal one being the Federal Commission Act. The principal provisions of this act have to do with the regulation of trade practices.

The Federal Commission is appointed by the President and may be of any number not exceeding seven years. It is organized into divisions, and that having to do with drug products is known as the Medical Advisory Division.

The principal power of the Federal Trade Commission with respect to drugs lies in section 15 of the Federal Trade Commission Act which was amended by the Wheeler-Lea Act in 1938 giving the Commission control over the advertising of *Foods, Drugs, and Cosmetics*. Although the Commission has broad power to prevent the dissemination of false or misleading advertising to the general public, this power is circumscribed with respect to advertisements directed to the medical profession. The Act states "No advertisement of a drug shall be deemed to be false if it is disseminated only to members of the medical profession, contains no false representations of a material fact, and includes, or is accompanied in each instance by truthful disclosure of, the formula showing quantitatively each ingredient of such drug."

The enforcement of the Federal Trade Commission Act rests with the Commission. Trial of issues involved in violations is held before a Trial Examiner who reports his findings to the Commission. Final disposition of the case rests with the Commission. Violations of Commission cease and desist orders or appeals from Commission orders are considered by the Federal Courts. In many instances controversies may be settled by stipulations between the Commission and respondents.

The United States Public Health Service. Among the many functions of the United States Public Health Service is the regulation of biological products. The Division of Biologics Control of the National Institute of Health administers that part of the Public Health Service Act of 1944 which incorporates the former Viruses, Serums, Toxins and Analogous Products Act.

The control exercised by the Public Health Service Act extends only to biologic products which are defined as 'any virus, therapeutic serum, toxin, antitoxin, or analogous product applicable to the prevention, treatment or cure of diseases or injuries of man.' By further definition the term 'biologic products' is extended to cover trivalent arsenical compounds. Pentavalent arsenical compounds are controlled under the Federal Food, Drug and Cosmetic Act by administrative agreement between the Public Health Service and the Food and Drug Administration.

The control exercised by the Public Health Service over biologic products is through the inspection and licensing of establishments producing such products and by the examination and licensing of the products themselves. It is illegal therefore to produce any biologic product in an establishment which has not been duly licensed by the Public Health Service or to ship in interstate commerce any biologic product for which a license has not been issued and which is not effective at the time of shipment.

In order for a biologic product to be licensed under the provisions of the Public Health Service Act it must meet the standards prescribed by the Division of Biologics Control of the National Institute of Health and each batch must be tested for compliance with these standards. The labels of these products must bear the proper name of the product, the name, address and license number of the manufacturer, the lot number and the expiration date. Under certain conditions and in the case of certain products additional information may be required to appear on the label.

The United States Treasury Department. The Bureau of Narcotics of the United States Treasury Department administers the Harrison Narcotic Act. This Act is part of the Internal Revenue Code and is primarily a taxing measure. The Act provides for the payment of certain taxes and the affixing of revenue stamps to lots of narcotic drugs.

Under the Harrison Narcotic Act, opium, cocoa leaves or any derivatives thereof or marihuana or any derivative thereof

is defined as being subject to the Act. Furthermore, by an amendment passed in 1946, the President may proclaim a drug as a finding by the . . . and an opportunity . . . within the purview . . . provision, the drug . . . the Act on July . . .

Although a tax measure, the Harrison Narcotic Act prescribes rigid controls over the transportation and distribution of narcotic drugs. Only physicians duly licensed under this Act may prescribe these drugs, and the form of such prescriptions and their handling is set forth in considerable detail.

The Post Office Department: The Fraud section of the post office under the direction of the Solicitor enforces the law pertaining to the fraudulent use of the mails. The use of the United States mails is a privilege and not a right and may be denied to those who use it for the purpose of defrauding the public. Therefore, the solicitation of customers and the shipping via the mails of drugs for which fraudulent claims are made may be the basis for the issuance of a "fraud order" and the suspension of all mail service to the guilty party. Determination of the guilt is made by the Solicitor after a hearing before him in which the facts are presented. Repeated violations or efforts to avoid compliance with such fraud orders may lead to criminal prosecution in the Federal Courts.

The United States Pharmacopoeial Convention: Under the General Committee on Revision, the United States Pharmacopoeial Convention issues at five-year intervals (formerly ten-year intervals) the United States Pharmacopoeia. The United . . . composed of . . . schools, state . . . ciations, the . . . pharmaceutical Association, the American Chemical Society, and many other scientific and trade associations and also various interested federal bureaus and departments.

Under authority of the Federal Food, Drug, and Cosmetic Act, the United States Pharmacopoeia is an official standard for the products described therein. Products are accepted for inclusion in the Pharmacopoeia by the Committee on Revision on the basis of demonstrated therapeutic value or pharmaceutical necessity.

The American Pharmaceutical Association: The National Formulary is issued by the Committee on the National Formulary elected by the Council of . . . sation. Admission of produ . . . based upon therapeutic value . . . of the drug and the apparent . . . tain drugs not necessarily widely used.

Under authority of the Federal Food, Drug and Cosmetic Act, the National Formulary is an official compendium, and

drugs described therein must meet the standards set forth in that publication

Preparations Specially Exempted from Council Consideration

Acetylsalicylic Acid
Ammonium Chloride

Dextrose Solution

Neocinchophen

Oxygen

Oxygen Carbon Dioxide Mixtures

Papaverine Hydrochloride

Pentobarbital Sodium

Quinine and Urea Hydrochloride

Salicylic Acid

Sodium Biphosphate

Isotonic Sodium Chloride Solution

Sodium Citrate

Sodium r-Lactate One-Sixth Molar

Sodium Salicylate

Strophanthin

Totaquine

Tribasic Calcium Phosphate

Tribasic Magnesium Phosphate

Trioxymethylene (Paraformaldehyde U S P X)

Table of Metric Doses with Approximate Apothecary Equivalents

The approximate dose equivalents in the following table represent the quantities which would be prescribed, under identical conditions, by physicians trained, respectively, in the metric or in the apothecary system of weights and measures.

When prepared dosage forms such as tablets, capsules, pills, etc. are prescribed in the metric system, the pharmacist may dispense the corresponding approximate equivalent in the apothecary system, and vice versa. This does not, however, authorize the alternative use of the approximate dose equivalents given below for specific quantities on a prescription which requires compounding, nor in converting a pharmaceutical formula from one system of weights or measures to the other system; for such purposes exact equivalents must be used (see U. S. P. XIII Table, page 913).

<i>Weights</i>	
Metric	Approximate Apothecary Equivalents
30 Gm. \approx	1 ounce
15 Gm. \approx	4 drachms
10 Gm. \approx	2½ drachms
7 5 Gm. \approx	2 drachms
6 Gm. \approx	90 gr.
5 Gm. \approx	75 gr.
4 Gm. \approx	60 gr. (1 drachm)
3 Gm. \approx	45 gr.
2 Gm. \approx	30 gr. (½ drachm)
1 Gm. \approx	15 gr.
0 75 Gm. \approx	12 gr.
0 6 Gm. \approx	10 gr.
0 5 Gm. \approx	7½ gr.
0 45 Gm. \approx	7 gr.
0 3 Gm. \approx	5 gr.
0.25 Gm. \approx	4 gr.
0 2 Gm. \approx	3 gr.
0.15 Gm. \approx	2½ gr.
0.12 Gm. \approx	2 gr.
0 1 Gm. \approx	1½ gr.
75 mg. \approx	1¼ gr.
60 mg. \approx	1 gr.
50 mg. \approx	¾ gr.
40 mg. \approx	⅔ gr.
30 mg. \approx	½ gr.
25 mg. \approx	⅜ gr.
20 mg. \approx	⅓ gr.
15 mg. \approx	¼ gr.
12 mg. \approx	⅕ gr.
10 mg. \approx	⅙ gr.

Table of Metric Doses with Approximate Apothecary Equivalents—Continued

Weights

Metric	Approximate Apothecary Equivalents
8 mg	= $\frac{1}{8}$ gr
6 mg	= $\frac{3}{40}$ gr
5 mg	= $\frac{1}{12}$ gr
4 mg	= $\frac{1}{16}$ gr
3 mg	= $\frac{1}{60}$ gr
1.5 mg	= $\frac{1}{40}$ gr
1 mg.	= $\frac{1}{60}$ gr
0.8 mg	= $\frac{1}{80}$ gr
0.6 mg	= $\frac{1}{100}$ gr
0.5 mg	= $\frac{1}{120}$ gr
0.4 mg	= $\frac{1}{150}$ gr
0.3 mg	= $\frac{1}{200}$ gr
0.25 mg	= $\frac{1}{250}$ gr
0.2 mg	= $\frac{1}{300}$ gr
0.15 mg	= $\frac{1}{400}$ gr
0.1 mg	= $\frac{1}{600}$ gr

Liquid Measures

Metric	Approximate Apothecary Equivalents
1000 cc.	= 1 qt.
750 cc	= $1\frac{1}{2}$ pt
500 cc.	= 1 pt.
250 cc	= 8 fl oz
200 cc	= 7 fl oz
100 cc	= $3\frac{1}{2}$ fl oz
50 cc.	= $1\frac{3}{4}$ fl oz
30 cc.	= 1 fl oz
15 cc.	= $\frac{1}{2}$ fl oz
10 cc	= $2\frac{1}{2}$ fl drachm
8 cc	= 2 fl drachm
5 cc	=
4 cc	= 1 fl drachm
3 cc	= 45 min
2 cc	= 30 min
1 cc	= 15 min
0.75 cc.	= 12 min
0.6 cc.	= 10 min.
0.5 cc	= 8 min.
0.3 cc.	= 5 m n.
0.25 cc	= 4 min.
0.2 cc	= 3 min
0.1 cc.	= $1\frac{1}{2}$ min.

NOTE—A cubic centimeter (cc) is the approximate equivalent of a milliliter (ml)

The Council on Pharmacy and Chemistry has voted to use exclusively the metric system in any publication for which it

has sole responsibility. For this reason a table of equivalents will be provided in each book for those who are familiar only with the apothecary system.

Formerly almost every country had its own system of weights and measures, a practice which resulted in much confusion. The one system which is used almost universally and exclusively in the exact sciences is the metric system, which is based on the decimal system and has for its units the meter and the gram. Other systems still enjoying some popularity, albeit decreasing popularity, are the Apothec.

in prescriptions, the Avoird used in commerce, and the Measure, which is not to be confused with the British Imperial System. Examples of

Apothecaries—grain,

60 grains) Troy ounce

—grain, ounce (437½

grains) and the ton

fluidrachm (60 minims)

minims), pint (16 fl

fairly accurate conversion:

1 Gm.	= 15.43 grains
1 Gm.	= 0.2572 dram
1 Gm.	= 0.03215 Troy ounce
1 Gm.	= 0.03527 Avoirdupois ounce
1 Gm.	= 0.0022 Avoirdupois pound

1 grain	= 0.0648 gram (Gm.)
1 grain	= 64.8 milligrams (mg.)
1 dram	= 3.888 grams (Gm.)

1 Troy or Apothecary ounce	= 31.1 grams (Gm.)
1 Avoirdupois ounce	= 28.35 grams (Gm.)
1 Avoirdupois pound	= 453.6 grams (Gm.)

1 cubic centimeter	= 16.23 minims
1 milliliter	= 16.23 minims
1 milliliter	= 0.2705 fluid dram
1 milliliter	= 0.0338 fluid ounce
1 milliliter	= 0.00211 pint
1 milliliter	= 0.000264 gallon

1 minim	= 0.06161 cubic centimeters (cc.)
1 fluid dram	= 3.6966 cubic centimeters (cc.)
1 fluid ounce	= 29.57 cubic centimeters (cc.)
1 pint	= 473 cubic centimeters (cc.)

may cause greater errors; every one should remember that a minim does not necessarily equal one drop; a drop will vary with the viscosity and surface tension of the fluid and the nature of the dropping container. A teaspoon will hold from 4 cc. (1 fluid dram) to 7 cc., a dessert spoon from 9 to 14 cc., a

APOTHECARIES, METRIC EQUIVALENTS

11

tablespoon from 15 to 22 cc, a wine glass from 50 to 90 cc.,
a teacup from 125 to 240 cc. and a tumbler from 200 to 300 cc.

The following table of approximations may be convenient for
translating pounds into kilograms

11 pounds = 5 kilograms	110 pounds = 50 kilograms
22 pounds = 10 kilograms	132 pounds = 60 kilograms
33 pounds = 15 kilograms	154 pounds = 70 kilograms
44 pounds = 20 kilograms	176 pounds = 80 kilograms
55 pounds = 25 kilograms	198 pounds = 90 kilograms
66 pounds = 30 kilograms	220 pounds = 100 kilograms
88 pounds = 40 kilograms	242 pounds = 110 kilograms

M. R

SECTION A

1

Agents Used in Allergy

This chapter includes agents used primarily in the diagnosis or treatment of allergic conditions. It thus comprises antigenic

chapter on Autonomic Drugs.

ALLERGENIC PREPARATIONS

Allergenic preparations are extracts, or solutions of various substances to which patients may become sensitive. These preparations are used for diagnosis and treatment of allergic conditions.

fibers used in clothing or in upholstery; from plants, fungi, bacteria, and from a variety of other substances to which patients may become sensitive.

stances in class (a) may often be determined by means of the so-called patch test. Sensitivity to substances in class (b) may often be determined by the so-called scratch test or by intradermal administration.

Solutions of allergens may deteriorate with age so it is necessary that they be used as the physician directs. They are determined by the regulat and must be stored at a the council requires that

as to avoid contamination and that their sale shall be authorized by the Federal Security Agency under the law governing the sale of biologic products. The council requires that the identity of any preservative used in accepted allergenic preparations be declared on the label.

Actions and Uses.—Allergenic preparations may be used for prophylaxis in instances of hay fever or pollen asthma by employing a series of suitably graded doses of specific pollen extracts up to and through the hay fever season, or for the treatment of hay fever by intracutaneous inoculation with suitable doses. In perennial asthma or rhinitis, if the offending substance can be determined by history or skin tests, patients may be treated by subcutaneous inoculations. Extracts of foods may be used to determine specific sensitivities to food but are not satisfactory for the treatment of these sensitivities.

Dosage.—No uniform method of standardization has been adopted. Two methods are acceptable, first standardization by the nitrogen content of the extract, and second standardization by amount of pollen or protein in the extract. The sensitivity of various patients is extremely variable so that the tolerance varies widely. For treatment graduated series of doses are supplied by the manufacturer. Most patients tolerate 10 to 15 mg. of dry allergens.

There should be no reaction or only a minimal wheal following this test.

Cutaneous tests, whether scratch, patch or intradermal, should be performed in accordance with an accepted procedure, and the interpretation of any such tests should only be undertaken by an individual who has had adequate experience under a competent instructor.

Food, Epidermal and Other Extracts

THE ARLINGTON CHEMICAL COMPANY

Food, Epidermal and Incidental Allergens: All of the items in lists A and B are marketed, for cutaneous testing, in vials containing. For foods and incidentals, 50 mg.; for epidermals, 25 mg.; and for furs, 15 mg. of dry allergens. In addition, the items in list A are marketed as extracts in hyposensitization sets of four 5 cc. vials, one each of four concentrations. In the case of food and dust extracts, these concentrations are 1:10,000, 1:5,000, 1:1,000 and 1:500. In the case of epidermal and incidental extracts, the concentrations are 1:100,000, 1:10,000, 1:1,000 and 1:500. Concentrations of 1:500 (and stronger solutions of certain items) are also marketed in 5 and 10 cc. vials. For intradermal testing 1, 3, 5 and 10 cc. vials of 1:500 solutions are available

List A—Foods: *Almond*,¹ *Apple*,⁴ *Apricot*,⁴ *Asparagus*,¹⁰ *Banana*,¹⁰ *Barley*,¹⁰ *Bass (Sea)*,² *Bean*,¹⁰ *Beef*,¹⁰ *Beet*,¹⁰ *Blackberry*,⁵ *Black-Eyed*

Pea,¹⁰ Black Walnut,¹ Bluefish,² Bran (wheat),¹⁰ Brazil Nut,¹ Broccoli,¹⁰
 Brussel Sprouts,¹⁰ Buckwheat,¹⁰ Cabbage,¹⁰ Cantaloupe,⁶ Carp,² Carrot,⁴
 Casein,¹¹ Cashew Nut,¹ Cauliflower,¹⁰ Celery,¹⁰ Cheese (American),⁸
 Cheese (Roquefort),⁸ Cheese (Swiss),⁸ Cherry,¹⁰ Chicken,¹⁸ Cinnamon,¹⁰
 Clam (Hard),² Clam (Soft),² Cocoa,¹⁰ Coconut,¹ Codfish,² Coffee,¹⁰
 Corn,¹⁰ Crab,² Cranberry,¹⁰ Cucumber,⁴ Date,⁶ Duck,¹⁰ Egg Plant,⁴ Egg
 white,⁷ Egg (whole),¹⁰ Egg (yolk),⁸ Fig,⁸ Flounder,² Garlic,¹⁰ Gelatin,⁷
 Ginger,¹⁰ Goose,¹⁰ Grape (Raisin),⁴ Grapefruit,⁴ Haddock,² Halibut,²
 Herrings,² Hops,¹⁰ Lactalbumin,⁸ Lamb,¹⁰ Lemon,⁴ Lettuce,¹⁰ Lima
 Bean,¹⁰ Liver (Bovine),¹⁰ Lobster,² Mackerel,² Malt,¹⁰ Milk (Cow),⁷
 Milk (Goat),⁷ Mushroom,¹⁰ Mustard,¹⁰ Oat,¹⁰ Olive,¹⁰ Onion,¹⁰ Orange,⁴
 Oyster,² Paprika,¹⁰ Parsley,¹⁰ Pea,¹⁰ Peach,⁴ Peanut,¹ Pear,¹⁰ Pecan,¹
 Pepper (Black),¹⁰ Pepper (red and green),⁴ Perch,² Pike,² Pineapple,¹⁰
 Pork,¹⁰ Potato,¹⁰ Prune (Plum),⁴ Pumpkin,⁴ Quince Seed,⁴ Radish,⁴

List B—Foods Allspice,¹⁰ Artichoke,¹⁰ Bass (Black),² Blueberry,⁶
 Butterfish,² Calves' Brains,¹⁰ Cassaba,⁴ Catfish,² Celery Cabbage (Pet
 tes),¹⁰ Cheese (Camembert),⁸ Cheese (Gorgonzola),⁸ Cheese (Lim
 burger),⁸ Cheese (Parmesan),⁸ Chestnut,¹ Chick Pea or Garbanzo,¹⁰

Allergen extracts Arlington, are prepared as follows. A weighed amount of the dried protein material, prepared as indicated below, is suspended in twentieth normal sodium hydroxide solution. The suspension

The intermediate and finished dilution products are tested for sterility according to the methods required by the U. S. Public Health Service.

The dried protein material used in the preparation of the extracts marked 1 is prepared as follows: The hard shells are removed; nuts are ground and extracted with carbon tetrachloride or acetone to remove oils. The residue is extracted with tenth normal sodium hydroxide solution. The extract is neutralized with diluted hydrochloric acid and the resulting precipitate collected, dried and sifted.

The dried protein material used in the preparation of the extracts marked 2 is prepared as follows: The edible portion is separated from the nonedible parts (scales, bones and so on) and finely ground. The

and ether and then ground and sifted.

The dried protein material used in the preparation of the extracts marked 4 is prepared as follows: The seeds are separated and the material chopped fine. An extract is made, sufficient tenth-normal sodium hydroxide solution being used to make the mixture alkaline to litmus. The extract is filtered and neutralized and the resulting precipitate collected, dried and sifted.

The dried protein material used in the preparation of the extracts marked 5 is prepared as follows: The material is chopped and after mixing with thymol is spread on trays to dry. The dried material is ground fine and extracted with tenth normal sodium hydroxide solution. The extract is neutralized with diluted hydrochloric acid and the resulting precipitate collected, dried and sifted.

The dried protein material used in the preparation of the extract marked 6 is prepared as follows: Skimmed milk is diluted with two volumes of distilled water. Diluted hydrochloric acid is added until the casein settles out. The casein is filtered off and the filtrate neutralized and concentrated in vacuo. Ammonium sulfate is added to saturation point and the precipitate redissolved in distilled water.

The dried protein material used in the preparation of the extracts marked 7 is prepared as follows: The material is dissolved in or diluted with distilled water. The solution is filtered if necessary and the protein precipitated with acetone. The precipitate is washed with acetone, dried, ground and sifted.

The dried protein material used in the preparation of the extract marked 8 is prepared as follows: The five protein fractions present in and separately prepared from wheat flour are mixed.

The dried protein material used in the preparation of the extract marked 9 is prepared as follows: Wheat flour is extracted with distilled water. The extract is collected, filtered clear and made slightly acid. It is then heated to 65° C and the precipitate filtered off, dried and sifted.

The dried protein material used in the preparation of the extract marked 10 is prepared as follows. The filtrate obtained after removing wheat leucosin is concentrated in vacuo. Four volumes of acetone are added and the resulting precipitate separated, dried, ground and sifted.

The dried protein material used in the preparation of the extract marked 11 is prepared as follows: Wheat flour is extracted with distilled water to remove the leucosin and proteose; the residue remaining is then extracted with 10 per cent sodium chloride solution. The extract is placed in a dialyzer until the precipitate settles out. The precipitate is washed with water, dried and sifted.

The dried protein material used in the preparation of the extract marked 12 is prepared as follows: The residue of wheat flour remaining after the removal of leucosin and proteose is extracted with sodium

extract
distilled
alcohol
sodium
chloride

The dried protein material used in the preparation of the extracts marked 14 is prepared as follows. The material is extracted with tenth normal sodium hydroxide solution. The extract is neutralized with diluted hydrochloric acid and the precipitate collected, dried and sifted. The filtrate is placed in a dialyzer until it is salt free and then concentrated in vacuo. The concentrate is precipitated with acetone, dried and sifted. Both fractions are then mixed.

The dried protein material used in the preparation of the extract marked 15 is prepared as follows. The material is dissolved in five volumes of distilled water and then centrifuged. The supernatant liquid is discarded, the residue is dried and powdered.

The dried protein material used in the preparation of the extracts marked 16 is prepared as follows. Equal parts of the egg white and egg proteins are mixed.

The dried protein material used in the preparation of the extract marked 17 is prepared as follows. Fresh skimmed milk is diluted with two volumes of distilled water. Diluted hydrochloric acid is added until the casein separates out. The casein is redissolved in sodium hydroxide solution and reprecipitated with diluted hydrochloric acid. It is then washed, dried, ground and sifted.

The dried protein material used in the preparation of the extracts marked 18 is prepared as follows. After removal of feathers, bones and the like any excess fat is trimmed off. The meat is collected and chopped fine. The material is then extracted with tenth normal sodium hydroxide solution. The extract is neutralized with diluted hydrochloric acid and the resulting precipitate collected, dried and sifted.

The dried protein material used in the preparation of the extracts marked 19 is prepared as follows. The material is chopped thoroughly or reduced to a fine powder by grinding. Where excess oil or fat is present this is removed by treatment with acetone or carbon tetrachloride. The material is then extracted with tenth normal sodium hydroxide solution. The extract is then neutralized with diluted hydrochloric acid and the resulting precipitate collected, dried and sifted.

The extracts marked 20 are prepared by the same method used in the preparation of pollen extracts Arlington.

ENDO PRODUCTS INC.

Allergenic Extracts Diagnostic. The following extract is marketed in packages of a single vial, with accompanying applicator containing 1 cc. of a 1:200 solution (0.5 per cent) of the original extract in 50 per cent glycerin.

House Dust (Purified) Concentrate

This extract, for use by the scratch method and cutaneous testing, is prepared in much the same manner as the allergenic extract Endo for treatment just described. The procedure is the same up to the point of dialysis, whereupon the extract for diagnosis undergoes the following treatment. To the solution obtained immediately before dialysis ammonium sulfate is added (60 Gm. per hundred cubic centimeters). The coagulated material is centrifuged. The separated solid is dissolved in one half the original volume of distilled water and the ammonium sulfate precipitation is repeated. The solid separated by centrifugation is suspended in a small volume of water and dialyzed until the solution in the sac does not respond to tests for the sulfate ion. The dialyzed solution is centrifuged to remove a small amount of suspended solids and the solution is adjusted (by vacuum distillation at low temperature if necessary) to contain 1 per cent of dissolved solids. Sufficient sodium chloride is added to yield a 1.8 per cent solution with respect to sodium chloride. The solution is diluted with an equal volume of glycerin and filtered through a Seitz filter. This 0.5 per cent solution constitutes the allergenic extract purified house dust concentrate for diagnosis by scratch testing.

Allergenic Extracts Therapeutic. The following extract is marketed in treatment set packages of four 10 cc. vials containing, respectively 1 cc. of a 2.5 per cent, 0.25 per cent, 0.025 per

cent and 0.0025 per cent dilution of the original extract in glycerosaline solution (50 per cent glycerin) and four 10 cc. vials containing 9 cc. of diluting fluid (0.4 per cent phenol in isotonic

House Dust (Purified Concentrate).

Allergenic extract house dust (purified concentrate)-Endo is prepared from dust obtained from mattresses and household furniture.

A mixture of 1 part by weight of house dust and 2 parts by volume of distilled water is covered with toluene and extracted while stirring, at 0 to 5 C. for seventy-two hours. The aqueous extract is separated

volumes of this aqueous solution are treated with 2 volumes of acetone, mixed thoroughly and centrifuged. The liquid is reserved. The residue is washed with a small amount of a 40 to 60 per cent V/V acetone-

filling into sterile vials by aseptic technic.

HOLLISTER-STIER LABORATORIES

on weight volume basis; the intradermal extract on a nitrogen basis (micro-kjeldahl method)

Allergenic extracts—Hollister-Stier for scratch testing are prepared by extracting for five days at 37° C. one part of the dried protein material with ten parts of a menstruum which is composed of 50 per cent of glycerine by weight, 5 per cent of sodium chloride and 45 per cent of distilled water. The extract is clarified and sterilized by Seitz filtration. The finished product represents a 1 to 10 dilution of the original substance.

The material for intradermal testing is extracted in a buffered saline

solution, containing 1:10,000 Merthiolate as a preservative. The extract is clarified and sterilized by Seitz filtration. The nitrogen content of the extract is determined and then diluted with buffered saline to the required strength.

PARKE, DAVIS & COMPANY

Allergenic Extracts, Diagnostic. Protein extracts derived from food, plant, bacterial and other proteins in the form of paste, the base of which is a mixture of glycerin and glycerite of starch. One part of paste represents one part of original material. The extracts afford a convenient means of carrying out the diagnostic scratch test. They are supplied in collapsible tubes containing 1.5 Gm. of material, enough for approximately 50 tests.

Group Allergenic Extracts, Diagnostic. A mixture of equal parts of two or more protein extracts diagnostic. P. D. & Co., supplied in collapsible tubes containing 1.5 Gm. of the mixture. The protein constituents of each group are selected on the basis of their class relationships.

WYETH, INCORPORATED

Protein Extracts Diagnostic. These extracts for the diagnosis of protein sensitivity by the intracutaneous method are supplied in 1 cc. size cartridge ("Tubex") vials containing sufficient protein material of appropriate dilution for twenty to thirty tests. The test sets are accompanied by a suitable cartridge syringe, sterile needles and three cartridge vials each of epinephrine hydrochloride solution, buffered saline solution and distilled water. After injection of each extract the needle should be flushed with distilled water to avoid contamination with the extract used previously.

Extracts marketed in dilution representing 0.005 mg. of nitrogen per cubic centimeter.

Apple, Apricot, Artichoke, Asparagus, Banana, Beef, Berries, Blackberry, Broccoli, Cabbage, Cantaloupe, Carrot, Cauliflower, Celery, Cherry, Chicken, Cucumber, Dates, Endive, Fig, Garlic, Grape, Grapefruit, Green Pea, Leek, Lemon, Lentil, Lettuce, Mushroom, Mutton, Olive, Onion, Orange, Parsley, Peach, Pear, Pepper (Green), Pineapple, Plum, Pork, Potato (Sweet), Potato (White), Prune, Pumpkin, Radish, Raspberry, Rhubarb, Spinach, Squash, Strawberry, Tomato, Turnip, Watercress, Watermelon.

Extracts marketed in dilutions representing 0.01 mg. of nitrogen per cubic centimeter.

Alfalfa (Hay), Bay Leaves, Bran, Chicken Feathers, Cinnamon, Clove, Coffee, Corn (Sweet), Duck Feathers, Eggs, Goat Hair, Goose Feathers, Hops, Kidney Bean, Lactalbumin, Milk (Cheese), Prunes, Oats, Rice, Rice Powder, Rye, Tea, Thyme, Wheat, Wool.

Extracts marketed in dilutions representing 0.005 mg. of nitrogen per cubic centimeter.

Brazil Nut, Cashew, Nut, Chestnut, Cocoa (Chocolate), Hazel Nut, Hickory Nut, Lima Bean, Navy Bean, Pea, Pecan, Pistachio, Soy Bean, String Bean.

Extracts marketed in dilutions representing 0.001 mg. of nitrogen per cubic centimeter.

Alder, Almond, Anise Seed, Ash (Oregon), Ash (White), Barley, Bass.

Penicillium mixture—containing equal parts of *P. camemberti*, *P. chrysogenum*, *P. digitatum*, *P. notatum*, *P. roqueforti*.

Trichophyton mixture—containing equal parts of *T. gypsum*, *T. interdigitale*, and *Epidermophyton inguinale*.

Fungus Allergens Arlington are made according to a standard method, viz., grown in a peptone-cerulose-yeast extract media, collected by filtration, washed with acetone, and ether and dried.

Fungus Allergen Extracts-Arlington are prepared as follows: (directions for preparation of 1000 cc. of extract 1:20 concentration).

Fifty grams of dried fungus material are suspended in 800 cc. of N/20 sodium hydroxide, and the suspension is placed on the shaking machine for four hours. The suspension is centrifuged and decanted, and the residue is exhausted by gravity filtration until the total volume is 850 cc. Ethyl alcohol (95 per cent) is added to the alcoholic solution, and the solution is rendered clear. The reaction of the solution is adjusted to pH 8.3 by the addition of either hydrochloric acid, or sodium hydroxide. Tricresol in the proportion of 0.4 per cent is added, and the solution sterilized by filtration through a Berkefeld filter. The finished products are placed on sterility tests, and mouse test according to the methods required by the U. S. Public Health Service.

From this 1:20 extract, necessary dilutions are prepared aseptically with a diluent of sterile phosphate buffer containing 14 per cent alcohol by volume and 0.4 per cent tricresol. The intermediate and finished products are tested for sterility according to the methods required by the U. S. Public Health Service.

Pollen Extracts

ABBOTT LABORATORIES

Concentrated Pollen Extracts: 2 cc. and 5 cc. vials.

U. S. patent 1,977,803 (Oct. 23, 1934; expires 1951).

Annual Sage; Arizona Ash; Ash; Bermuda Grass; Black Walnut; Biennial Sage; Blue Grass; Box Elder; Burweed; Marsh Elder; Canada Blue Grass; Cocklebur; Corn; Cosmos; Coastal Sagebrush; Cottonwood; Crab Grass; Dandelion; English Plantain; Elm; False Ragweed; Giant Ragweed; Goldenrod; Goose Grass; Hemp; Hickory; Johnson Grass; Lamb's Quarters; Marsh Elder; Mixed Grass (Blue Grass, Timothy, Orchard Grass, Red Top, and Sweet Vernal Grass in equal parts); Mixed Ragweed (Ambrosia elatior and Ambrosia trifida); Mountain Cedar; Mugwort; Oak Concentrated; Orchard Grass; Ox-Eye Daisy; Palmer's Amaranth; Plantain; Prairie Sage; Quailbrush; Redroot Pigweed; Red Sorrel; Redtop; Russian Thistle; Sagebrush; Short Ragweed; Slender False Ragweed; Southern Ragweed; Spiny Amaranth; Sunflower; Sweet Vernal Grass; Sycamore; Timothy; Western Ragweed; Western Water Hemp; Yellow Dock; Yellow Fox-Tail.

Concentrated pollen extracts-Abbott are prepared by extracting dried pollen with a menstruum composed of 5 per cent of dextrose and 0.5 per cent of phenol in distilled water. The extract is clarified and sterilized by filtration. The finished liquid is a 3 per cent extract of the dried pollen, each cubic centimeter representing 0.03 Gm. of dried pollen (30,000 units).

Pollen Extracts: Extracts marketed in the following forms:

Tre
(1)
1,50
acc
ephedrine hydrochloride.

U S patent 1,977,803 (Oct 23 1934, expires 1951)

Mixed Grass (Timothy, June Grass Orchard Grass, Red Top and Sweet Vernal Grass in equal proportions), Ragweed (*Ambrosia elatior* and *Ambrosia trifida*)

Extracts marketed in special dilution sets

Mixed Ragweed Pollen Extract Decimal Dilution Set A mixture of equal parts of short and giant ragweed pollen extract marketed in packages of four vials containing respectively, 5 cc of a 1 10 000 dilution (100 pollen units per cubic centimeter), 5 cc of a 1 1 000 dilution (1 000 pollen units per cubic centimeter), and two 5 cc vials of a 1 100 dilution (10 000 pollen units per cubic centimeter)

Mixed Grass Pollen Extract Decimal Dilution Set A mixture of
per cubic centimeter)

* Pollen extracts Abbott are prepared by extracting dried pollen with a menstruum composed of 5 per cent of dextrose and 0.5 per cent of phenol in distilled water. The extract is clarified and sterilized by filtration. The finished liquid is a 3 per cent extract of the dried pollen each cubic centimeter representing 0.03 Gm. of dried pollen (30,000 units). Dilutions are prepared with additional menstruum.

Pollen Extracts Diagnostic: For skin testing the extracts are supplied in vials of 3 and 50 capillary tubes, each tube providing sufficient material for one scratch test.

THE ARLINGTON CHEMICAL COMPANY

1. The first step in the process is to identify the problem or issue that needs to be addressed. This involves gathering information and understanding the context of the problem.

In addition, the following pollen mixtures are available in treatment sets containing five 3 cc. vials of the same concentrations as indicated above for individual pollen hyposensitization sets; concentrations of 1:33, and 1:50 in addition to above are also available in 3, 5, and 10 cc. vials.

Timothy June (Blue) Grass, Orchard Grass and Red Top

Timothy, June (Blue) Grass, Orchard Grass, Red Top and Sweet Vernal Grass.

Bermuda Grass and Johnson Grass.

Timothy, June (Blue) Grass, Orchard Grass, Red Top and English Plantain.

Tall and Short Ragweeds.

and Cocklebur.

Cocklebur.

road, Cocklebur.

Burned Marshelder and Prairie Sage.

Tall and Short Ragweeds, Sunflower, Goldenrod, Cocklebur and Mugwort.

Tall and Short Ragweeds, June (Blue) Grass, Orchard Grass, Timothy, Red Top and Sweet Vernal Grass.

Tall and Short Ragweeds and Dust.

Hickory and Pecan.

Pollen extracts-Arlington are prepared by the following method:

Three parts of defatted pollen are extracted with 84 parts of phosphate buffer, pH 8.3, using 0.1 per cent cresol as preservative, for 24 hours. During the extraction period the suspension is kept at icebox temperature except for 2 hours during which it is mechanically shaken. Sufficient ethyl alcohol is added to the suspension to make the alcohol concentration of the final filtrate 14 per cent by volume. Extraction is then continued for another 24 hours with an additional 2 hours shaking. The mixture is filtered and to the filtrate tricresol is added to a concentration of 0.4 per cent. The pH is adjusted to about 8 and the clear solution is passed through a sterilizing filter. The sterile solution is a 1:33 pollen

BARRY ALLERGY LABORATORY, INC.

Allergenic Extracts: The following extracts are marketed

per cent phenol used as preservative.

Grass Mixture (Spring), (June Grass, Timothy, Red Top, Sweet Vernal Grass and Orchard Grass, in equal proportions); Ragweed (Large and Small Ragweed, in equal proportions).

the dried pollen in glycerine, 0.275 per cent, 0.0285 per cent of phenol. The original (30,000 pollen) is diluted to the 0.0285 per cent of phenol. The finished product is 0.0285 per cent of phenol.

CUTTER LABORATORIES

Allergenic Extracts: The following extracts are marketed in complete treatment set packages consisting of four vials

Acacia, Alder, Alfalfa, Alkali Rye, Alkali Weed, All Scale, Almond, Annual June Grass, Annual Saltbush, Ash, Aspen, Awnless Brome Grass, Barnyard Grass, Barley Wall, Barley, Field, Bent Grass, Bermuda Grass, Birch, Blue Grass, Canadian, Box Elder, Brome

HOLLISTER STIER LABORATORIES

Pollen Extracts: The following extracts are marketed in treatment sets of four vials containing, respectively 10, 100, 1,000 and 10,000 pollen units per cubic centimeter, preserved with 50 per cent glycerine, and in single vials of 1, 2, 5, 10 and 20 cc quantities

For diagnostic purposes these pollen extracts are marketed in regional sets containing 0.5 cc of each extract sufficient for eight or ten tests, and in single vials of 1 cc. The vials are fitted with rubber bulbs and glass droppers

Acacia, Alder, Alfalfa, Ash (White), Aspen, Atriplex, Awnless Brome Grass, Beech, Bermuda Grass, Blue Bunch Grass, Box Elder, Canada Blue Grass, Careless Weed, Cedar (Mountain), Cleat, Clover, Cocklebur, Corn, Cottonwood (Common), Crested Koeleria, Dandelion

Dock (Yellow); Eastern Ragweed; Elm; English Plantain; Fescue (Meadow); Giant Poverty Weed; Goldenrod; Johnson Grass; Kentucky Blue Grass; Kochia; Lamb's Quarters; Maple (Hard); Mugwort; Oak (White); Olive; Orchard Grass; Perennial Rye Grass; Pine (Yellow); Quack Grass; Redroot Pigweed; Redtop; Russian Thistle; Sage (Common); Sage June Grass; Sugar Beet; Walnut (En (Cultivated), Willow and Wormwood

Pollen	ed by extracting the dried
pollen	"	per cent of glycerine, 5 per
cent o	"	distilled water. The extract
is clar	"	ed liquid is a 5 per cent
extract	"	timeter representing 50,000
pollen	"	mg. of dried pollen.

NATIONAL DRUG COMPANY

Allergenic Extracts: The following pollen extract is marketed in packages of three 5 cc. vials representing, respectively, 2,500, 5,000, and 10,000 nitrogen units per cubic centimeter; and in single 5 cc. vial packages of 10,000 and 25,000 nitrogen units per cc. for maintenance dosage. Each package is accompanied by a 1 cc. vial, 150 units per cc. concentration, for preliminary

means of the
vidual capillary

The following preparations are marketed in 10 cc. and 15 cc. vial packages representing, respectively, 2,500, 5,000, 10,000 and 25,000 nitrogen units per cubic centimeter:

Ragweed (Giant and Dwarf Ragweed in equal parts), Mixed Grass (Timothy, 75 per cent; June Grass, Orchard Grass, Red Top, Rye, and Sweet Vernal Grass, each 5 per cent).

Allergenic extracts are prepared by the following method: The pollen is weighed and extracted with ether. After removal of the ether the material is mixed with the extracting liquid consisting of a 0.5 per cent sodium chloride solution containing approximately 0.28 per cent of sodium bicarbonate and 0.4 per cent of phenol and then covered with toluene. After four days, during which time the mixture is shaken once or twice daily, the supernatant fluid is decanted and the sediment mixed with a second portion of extracting fluid. As soon as the sediment has settled, the supernatant fluid is decanted and mixed with the first portion. The combined decanted fluid is then subjected to Berkefeld filtration and tested for sterility. The nitrogen content of the extract is determined and dilutions are prepared on a basis of 0.00001 mg. of nitrogen per unit.

PITMAN-MOORE CO., DIVISION OF ALLIED LABORATORIES, INC.

Allergenic Extracts: The following pollen extracts are marketed in single 5 cc vials containing 10,000 units per cubic centimeter and in packages containing one 5 cc. vial of the extract, together with three vials containing 4.5 cc. of sterile isotonic sodium chloride diluent for the preparation of solutions containing 1,000, 100 and 10 pollen units per cubic centimeter.

Mixed Grass (Sweet Vernal Grass, Blue Grass, Johnson Grass, Redtop and Timothy, in equal parts); Ragweed Pollens (Mixed) (Giant Ragweed and Short Ragweed, in equal parts).

Allergenic extracts Pitman Moore are prepared by the following method: The dried pollens are extracted with a menstruum containing an equal volume of glycerin and water, to each hundred cubic centimeters of which has been added sodium chloride 0.15 Gm., sodium bicarbonate 0.135 Gm., and sodium ethylmercuri thiosalicylate 10 mg. as a preservative. After extraction for generally two to three days, the extract is filtered and the residue is extracted again with the same menstruum. The extracts are then combined and the dried pollen.

U. S. STANDARD PRODUCTS COMPANY

Allergenic Extracts: The following pollen extracts are supplied in 5 cc. vial. In addition, two weed Combined of three vials, corresponding to the pollen per cubic centimeter of epinephrine hydrochloride solution. The following are the pollen tubes contained in each vial:

Alder (Tag), Alfalfa, Bermuda Grass, Red Top, Sweet Vernal, Ragweed (Common), Ragweed (W. in equal part), Sweet Vernal, Water Hemp, Dock, Box Elder, E. C. (Cyanthanthemum), Cottonwood, English Plantain, Grass, Orchard Grass, (equal parts), Elder, Mugwort, (root); Pine (Common), Ragweed (W. in equal part), Sweet Vernal, Water Hemp, Dock.

The following product is supplied in 5 cc. vials representing 30,000 pollen units per cubic centimeter and in packages of four 5 cc. vials representing, respectively, 100, 1,000, 10,000 and 100,000 pollen units per cubic centimeter:

Ragweed Combined (Giant and Common Ragweed in equal parts).

The following product is supplied in 5 cc. vials representing 30,000 pollen units per cubic centimeter

Grasses Combined (Bermuda, June Grass, Orchard Grass, Red Top, Sweet Vernal Grass and Timothy in equal parts)

Prepared by extracting the dried pollen with a menstruum containing 1% per cent. sodium chloride and 1% per cent. sodium bicarbonate.

Each 5 cc. vial contains 30,000 pollen units, one pollen unit

LEDERLE LABORATORIES, DIVISION AMERICAN CYANAMID CO.

Poison Ivy Extract in Almond Oil: 1 cc. vials.

Freshly gathered mature leaves of *Rhus toxicodendron* are macerated with acetone. The resulting extract is decolorized and dehydrated and then concentrated until the content of solid matter becomes 33 per cent. Five parts of this liquid are added to 95 parts of sterile almond oil containing 0.5 per cent of chlorobutanol and this solution is filtered.

MULFORD COLLOID LABORATORIES

Rhus Tox Antigen: Packages of four 1 cc. ampul vials. Each 1 cc. contains 7.5 mg. of substance dissolved in 35 per cent alcohol.

Freshly gathered mature leaves of *Rhus toxicodendron* are macerated with ethyl chloroformate, and phosphoric acid extract in an extract.

PARKE, DAVIS & COMPANY

Poison Ivy Extract: 1 cc. ampuls. A 15 per cent solution of poison ivy extract, *Rhus toxicodendron* (poison ivy—poison oak) antigen in almond oil.

The dried leaves of poison ivy (*Rhus toxicodendron*) are extracted with ethyl chloroformate, and phosphoric acid extract in an extract.

PITMAN-MOORE CO., DIVISION OF ALLIED LABORATORIES, INC.

Poison Ivy Extract with Sterile Diluent: 1 cc. vial, marketed in a package also containing three 0.9 cc. vials of sterile diluent consisting of a sterile isotonic salt solution containing procaine hydrochloride 0.5 per cent and chlorobutanol 0.4 per cent.

Extract contains 1 mg. of solid.

POISON IVY-POISON OAK EXTRACT COMBINED.—Ivoko (PITMAN-MOORE).—A combination of equal parts of the extracted solids of the dried leaves of poison ivy and oak prepared in accordance with requirements of the National Institute of Health.

Actions and Uses.—Poison Ivy-Poison Oak Extract Combined is used for the prevention of symptoms of contact with either of these plants.

Dosage—Parenteral injections of the number and volume recommended for the product used. The interval between doses is usually two weeks.

An extract standardized to contain 1 mg of total extracted solids (0.5 mg of each) per cubic centimeter is administered in an average dose of 0.1 cc. of the extract diluted to a volume of 1 cc. In hypersensitive persons, one twentieth of that dose should be used as a test dose and the dose then gradually increased to the average. It is administered at intervals of one to three weeks during exposure.

PITMAN-MOORE COMPANY

Ivoko Poison Ivy-Poison Oak Extract with Sterile Diluent—1 mg extracted solids per cc, 1 cc vials each packaged with six 0.9 cc vials of 0.5 per cent procaine hydrochloride in isotonic sodium chloride solution. Preserved with chlorobutanol 0.4 per cent as a sterile diluent.

POISON IVY-SUMAC EXTRACT.

dron vernix.

Dosage—Three injections of 0.1 cc, 0.2 cc and 0.4 cc on successive days.

BARRY LABORATORIES INC.

Poison Ivy-Sumac Extract Packages of four vials one

Preparation—

The only substance which is extracted with suitable solvents from the fresh leaves of *Rhus toxicodendron rodicum* and *Rhus toxicodendron vernix* is purified and decolorized. The resultant oily resin is dissolved in alcohol and standardized to represent a 1:500 dilution.

POISON OAK EXTRACT—A solution of a resin extracted from the fresh leaves of *Rhus diversiloba*.

Actions and Uses—Poison oak extract is used for the prevention of the symptoms of the dermatitis produced through contact with *Rhus diversiloba*.

Dosage—Parenteral injections of the number and volume recommended for the product used. The interval between doses is usually two weeks.

HOLLISTER STIER LABORATORIES

Poison Oak Extract Packages of five rubber stoppered vials, each containing 0.2 cc of alcoholic extract, in graduated

strengths with five vials of sterile salt solution for dilution immediately before administration.

Ten Gm. of mature leaves of *Rhus diversiloba* are dried, pulverized and extracted 72 hours in 100 cc. of absolute ethyl alcohol. The extract is decolorized, sterilized by filtration and diluted to proper strength.

LEDERLE LABORATORIES, DIVISION AMERICAN CYANAMID CO.

Poison Oak Extract in Almond Oil: 1 cc. vials.

Freshly gathered mature leaves of *Rhus diversiloba* are macerated with acetone. The resulting extract is decolorized and dehydrated and then concentrated until the content of solid matter becomes 13 per cent. Five parts of this liquid are added to 95 parts of sterile almond oil containing 0.5 per cent of chlorobutanol and this solution is filtered.

PITMAN-MOORE CO., DIVISION OF ALLIED LABORATORIES, INC.

Poison Oak Extract with Sterile Diluent: 1 cc. vial, marketed in a package also containing three 0.9 cc. vials of sterile diluent consisting of a sterile isotonic salt solution containing procaine hydrochloride 0.5 per cent and chlorobutanol 0.4 per cent.

Fresh leaves of *Rhus diversiloba*, dried at temperatures not exceeding 60 C., and sieved to remove stems and leaf midribs, are macerated with absolute ethyl alcohol, using 20 cc. of alcohol for each gram of dried leaves. The extract is filtered through paper, then diluted by adding absolute ethyl alcohol until each cubic centimeter of the final extract contains 1 mg. of solids.

POISON SUMACH EXTRACT.—A solution of a resin extracted from the fresh leaves of *Rhus venenata*.

Actions and Uses.—Poison sumach extract is used for the prevention of the symptoms of the dermatitis produced through contact with *Rhus venenata*.

Dosage.—For prophylaxis, two injections of 1 cc. each may be given, separated by an interval of two weeks.

MULFORD COLLOID LABORATORIES

Rhus Venenata Antigen: Packages of four 1 cc. ampul vials. Each cc. contains 7.5 mg. of substance dissolved in 35 per cent alcohol.

Freshly gathered leaves of *Rhus venenata* are extracted with ethyl

HISTAMINE-ANTAGONIZING AGENTS

The acceptance of the concept that histamine plays an important role in the production of the symptoms associated with allergic reactions and the demonstration that histamine may be released in the tissues by other mechanisms have led to the development of compounds which antagonize histamine. Among a group of such substances a number of ethylenediamine derivatives were found to possess such activity, but most of them were too toxic to be used therapeutically. In the last few years several new compounds, most of which are of the ethylenediamine series, were shown to be relatively nontoxic and useful in the symptomatic amelioration of some allergic phenomena. These compounds must, however, be regarded primarily as adjuncts and

pharmacologic and therapeutic actions common to all. These general attributes characteristic for the series will be briefly discussed here, while the major qualitative, quantitative and toxic differences will be separately pointed out in the monographs of each individual drug.

have antianaphylactic properties, but the doses required are greater than those necessary to inhibit histamine shock. All of these substances have local analgesic action. It has also been claimed by some that these chemical compounds diminish the capillary permeability from causes other than histamine.

The therapeutic effects of the antihistamine compounds are most evident in the nasal allergies. The symptoms of seasonal hay fever are more amenable to relief than those of perennial vasomotor rhinitis. The severity of the allergy, the severity and stage of the hay fever season and the nature of the hay fever symptoms have a bearing on the incidence and degree of relief. The mild hay fever, the first part of the season, the mild season, favorable weather conditions, localities with low pollen or mold spore counts, and predominantly sneezing symptoms are factors which increase the likelihood of relief. On the other hand, severe

action, but the usefulness of this effect is limited to bronchial spasm. It produces a high incidence of sedation when used in full therapeutic doses

Dosage.—The average adult dose is 50 mg. orally, three or four times daily.

PARKE, DAVIS & COMPANY

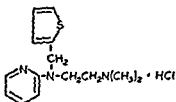
Capsules Benadryl Hydrochloride: 25 mg.

Elixir Benadryl Hydrochloride: 10 mg. per 4 cc., 473 cc. bottles. Each 100 cc. contains diphenhydramine hydrochloride 0.25 Gm., in an elixir containing alcohol, glycerin and water, with sugar, flavoring oils and added color.

Kapseals Benadryl Hydrochloride: 50 mg.

U. S. patent 2,421,714 (expires June 3, 1964); U. S. trademark 416,252.

METHA-
ene Hydroc
N'-(2-thenyl
formula for
follows:



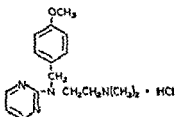
For tests and standards, see Section B.

Actions and Uses.—See general statement. Methapyrilene hydrochloride has a moderate therapeutic efficacy, and its sedative action is about equal to that of tripeleminamine hydrochloride. There is a moderate tendency to gastro-intestinal irritation

Dosage.—The average adult dose is from 50 to 100 mg. As with other antihistaminics, the dose should be the smallest which will relieve symptoms.

ABBOTT LABORATORIES

Tablets Thenylene Hydrochloride: 25 mg, 50 mg. and 0.1 Gm.



For tests and standards see Section B

Actions and Uses—See general statement. The therapeutic action of thonzylamine hydrochloride is qualitatively the same as with other members of the antihistaminic series but the frequency and degree of effectiveness is of a lower order. Its outstanding advantage is that it is tolerated better than the other compounds for sedation is less frequent and less severe.

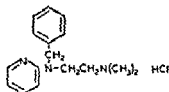
Dosage—The average adult dose is 100 mg.

WYETH INCORPORATED

Syrup Neohetramine 6.25 mg per cc 475 cc bottles

Tablets Neohetramine 25 mg 50 mg and 100 mg

TRIPLENNAMINE HYDROCHLORIDE—Pyri benzamine Hydrochloride (CIBA)—N N dimethyl N benzyl N (α pyridyl)ethylenediamine hydrochloride—Beta dimethyl aminoethyl 2 pyridyl benzyl ammonium chloride—The structural formula of tripeleennamine hydrochloride may be represented as follows



For tests and standards see Section B

Actions and Uses—See general statement. Tripeleennamine hydrochloride has excellent therapeutic effectiveness. The incidence of side reactions is low. Gastrointestinal irritation is common but not severe and nervous system stimulation occurs not infrequently.

Dosage—The average adult dose is 50 mg and when indicated larger doses of from 100 to 150 mg are tolerated by most persons.

CIBA PHARMACEUTICAL PRODUCTS INC

Elixir Pyribenzamine Hydrochloride 5 mg per cc 473 cc. bottles. Each 100 cc. contains tripeleennamine hydrochloride

0.5 Gm, in an elixir containing alcohol, glycerin and water, with syrup U. S. P., flavoring oils and added color.

Tablets Pyribenzamine Hydrochloride: 50 mg.

U. S. patent 2,406,594.

Analgesics

Analgesics are drugs used to relieve pain without producing loss of consciousness. The more potent of these are represented by morphine, its derivatives, and newer synthetic agents like meperidine, which have a central analgesic effect. The problem of analgesia was first used as a pyretic agent in para-

Quinine, the oldest of the antipyretics, is now used primarily as an antimalarial and will therefore be described with its derivatives in the chapter on Systemic Anti-Infective Agents employed chiefly for general anesthesia that may be used as analgesics are described in the chapter on Anesthetics.

OPIUM PRINCIPLES AND DERIVATIVES

Morphine is a complex derivative of phenanthrene. It contains two OH groups (one phenolic, the other alcoholic) in which the hydrogen can be substituted by either alkyl or acid radicals.

The more important alkyl esters are the monomethyl (codeine), the dimethyl (thebaine), and ethyl morphine. Heroin is the diacetyl derivative.

The nature of these radicals—whether acid or alcoholic, aromatic or aliphatic—modifies the actions, but only quantitatively. Replacement of one hydroxyl group (codeine) diminishes the narcotic action and increases the respiratory and tetanic action. When both OH groups are replaced by acids (diacetyl morphine), the narcotic effects are stronger than with codeine, and the tetanic action is weaker than with morphine.

Actions and Uses—The central actions of all these morphine derivatives are qualitatively identical, but they present quantitative differences which have some practical importance.

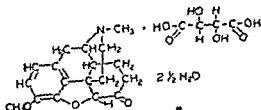
Morphine produces the strongest analgesic, hypnotic and intestinal effects, and the weakest stimulation of the opium alkaloids. It causes the greatest derangement of digestion. It and diacetyl morphine are most liable to induce a habit.

Codeine (methyl-morphine) is less narcotic, less constipating and less apt to induce tolerance and habit. It is, therefore, especially valuable in cough or, in other conditions in which the sedative action must be continued for some time and in patients who do not tolerate morphine.

Ethyl-Morphine seems to stand intermediate between morphine and codeine, in all respects. The hydrochloride is used as a sedative, but mainly for its special action on the conjunctiva.

Diacetyl-Morphine (heroin) closely approaches morphine of which it shares all the disadvantages, and over which it has no important advantage. It was originally introduced with the claim that therapeutic doses lessen the cough reflex and slow the respiration, but that the inspirations are deepened and more powerful. Independent workers, however, have shown that there is no real difference from morphine in these respects. It is now generally conceded that diacetyl-morphine is as effective as morphine in cough, but not more so; that it is rather less effective against dyspnea; and that it is more liable to produce habit and toxic effects.

DIHYDROCODEINONE BITARTRATE.—**Hycodan Bitartrate** (ENDO).—The hydrated bitartrate of dihydrocodeinone—The structural formula of dihydrocodeinone bitartrate may be represented as follows:



For tests and standards, see Section B.

Actions and Uses—Dihydrocodeinone bitartrate is essentially similar in action to codeine salts but is more active when compared with codeine on a weight basis and is also more addicting. It is useful primarily as an antitussive and may be used for this purpose in the same manner as codeine, over which it has no clearcut advantage.

Dosage—Adults, from 5 to 15 mg., 3 or 4 times within a 24-hour period. The higher dosage is rarely necessary. Children 2 years of age or older may be given one-half the adult dose; younger children one-quarter the adult dose.

ENDO PRODUCTS, INC.

Hycodan Bitartrate (Powder): 1 Gm., 5 Gm. and 10 Gm. bottles.

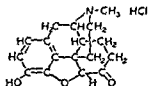
Syrup Hycodan Bitartrate: 5 mg. per 5 cc., 475 cc. and 3.74 liter bottles.

Tablets Hycodan Bitartrate: 5 mg

U S trademark 399 421

DIHYDROMORPHINONE HYDROCHLORIDE.

U. S. P.—Dilaudid Hydrochloride (BILHUBER KNOLL)—Dihydromorphinone hydrochloride differs essentially from morphine hydrochloride in that one of the hydroxyl groups of the latter has been replaced by a ketone group and the adjacent double bond has been removed by hydrogenation. The structural formula may be represented as follows



For description and standards see the U S Pharmacopeia under Dihydromorphinone Hydrochloride and Dihydromorphinone Hydrochloride Tablets

Actions and Uses—The base dihydromorphinone is closely allied both chemically and pharmacologically to morphine, having the analgesic property of morphine as well as its action on the respiratory system. Its action on the intestine is probably less marked than is that of morphine. It is more toxic than morphine and is clinically effective in doses which are considerably smaller than are necessary with morphine.

Hydrochloride—The hydrochloride of dihydromorphinone can depress the respiratory system. The hydrochloride of dihydromorphinone is very different from the hydrochloride of morphine. A clinical trial has not shown that dihydromorphinone hydrochloride is free from tolerance and addiction evoking properties and while it does not cause nausea, vomiting and other side effects, it is more potent than with morphine. It should be used with caution as a narcotic.

Dosage—As a sedative and for the relief of pain, the usual oral dose is 2.5 mg, in mild pain or cough, 1.3 mg may be given orally. The customary hypodermic dose is 2 mg. Clinically, the dose necessary to produce analgesia is about one fifth that of morphine.

BILHUBER-KNOLL CORP

Solution Dilaudid Hydrochloride: 2 mg per cc, 11 cc.

ampuls. Each cubic centimeter contains dihydromorphinone hydrochloride, 2 mg. in isotonic solution of sodium chloride.

Tablets Dilaudid Hydrochloride: 25 mg.

Compounding Tablets Dilaudid Hydrochloride: 32 mg. These tablets, each many times the average dose, are for use in compounding only.

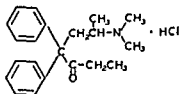
Hypodermic Tablets Dilaudid Hydrochloride: 1 mg., 1.3 mg., 2 mg., 3.2 mg. and 4 mg.

Rectal Suppositories Dilaudid Hydrochloride: 2.5 mg. dihydromorphinone hydrochloride in cacao butter base.

U. S. trademark 298,197.

NONOPIATE, ADDICTING ANALGESICS

METHADONE HYDROCHLORIDE—*Methadone hydrochloride* (4,4'-diamino-4,4'-diphenyl-1-methyl-2-propionyl-1-piperidine) formula may be represented as follows:



For tests and standards, see Section B.

Actions and Uses.—Methadone hydrochloride possesses, in general, a pharmacologic action similar to that of morphine. It is

slowly, and their peak intensity is less than after similar ad-

drugs are of importance. The drug has a satisfactory antitussive action.

Dosage.—Adults, 2.5 to 10 mg. depending on the intensity and every three 5 mg. orally

If the production of amnesia is desired, one of the barbiturates may be given when the cervix is dilated 4 or 5 cm or when the third dose of meperidine hydrochloride is administered. In the majority of cases this procedure will insure adequate amnesia for from four to six hours. When barbiturates are used with meperidine hydrochloride for this purpose they are effective in considerably smaller doses than when used alone.

WINTHROP-STEARNs, INC.

Demerol Hydrochloride (Powder): 15 Gm vials

Solution Demerol Hydrochloride: 50 mg per cc, 2 cc. ampuls and 30 cc vials

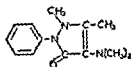
Tablets Demerol Hydrochloride: 50 mg and 100 mg

U S patent 2,167,351 (July 25, 1939, expires 1956) U S trademark 281,130

PYRAZOLON DERIVATIVES

The preparations in this group are used for their antipyretic and analgesic action and in general are subject to the same caution statements that govern the use of the phenetidan compounds. On taking small doses, some susceptible individuals experience nervous and circulatory depression, while after large doses instances of collapse have been reported. In the treatment of infectious fevers, they, as other antipyretics, should be cautiously employed. (See the general section, Para-amino-phenol Derivatives.) Serious and sometimes fatal granulocytopenia may appear, especially in susceptible individuals. The drug should be immediately withdrawn if a skin eruption, dizziness, throat irritation or chill occurs, it should not be administered in large doses or over a long period of time unless repeated leukocyte and differential blood counts are made at frequent intervals. The slightest untoward symptoms are indications for withdrawal of the drug and immediate leukocyte differential count.

AMINOPYRINE-U. S. P.—Pyramidon (WINTHROP-STEARNs) — Amidopyrine — 1-Phenyl 2,3-dimethyl 4-dimethylamino-5 pyrazolone (cf formula below) or, more properly, 1,5-dimethyl-2 phenyl-4-dimethylamino-3-pyrazolone. The structural formula may be represented as follows:



For description and standards see the U S Pharmacopoeia under Aminopyrine and Aminopyrine Tablets and The National Formulary under Aminopyrine Elixir

Actions and Uses.—Aminopyrine acts as an antipyretic and

menorrhoea or for any other purpose at or near the menstrual period. Special attention is called to the dangerous side actions mentioned in the article, Pyrazolon Derivatives.

Dosage.—From 0.3 to 0.4 Gm., most conveniently in the form of tablets, a single dose usually sufficing for twenty-four hours.

ABBOTT LABORATORIES

Tablets Aminopyrine: 0.325 Gm.

MERCK & Co, INC.

Aminopyrine (*Powder*): Bulk.

THE WM. S. MERRELL COMPANY

Tablets Aminopyrine: 0.3 Gm.

WINTHROP-STEARNs, INC.

Pyramidon (*Powder*): Bulk.

Elixir Pyramidon: 0.162 Gm. per 4 cc., in a menstruum containing alcohol 20 per cent.

Tablets Pyramidon: 0.13 Gm. and 0.325 Gm.

U. S. patent expired. U. S. Trademark.

SALICYLIC ACID COMPOUNDS

To avoid the disagreeable taste and gastric symptoms of salicylic acid, the structural formula of which is given below,



and its salts, esters of salicylic acid have been introduced. These esters are more or less insoluble, so that the salicyl radical is absorbed only in the intestine or after absorption into the blood.

gastric irritation when properly guarded by a bicarbonate. The taste, however, is much less objectionable than that of the simpler salicylate salts.

Compounds which hydrolyze to produce salicylic acid may be of the following types

1 Simple salts of salicylic acid e g sodium salicylate

2 Acyl esters of salicylic acid involving the phenolic hydroxyl group e g acetylsalicylic acid

3 Alkyl and aryl esters of salicylic acid involving the carboxylic group e g methyl salicylate and phenyl salicylate respectively

The acyl derivatives (acetylsalicylic acid type) possess a higher analgesic and antipyretic action than simple salicylate salts

The alkyl esters (methyl salicylate type) are absorbed readily from the skin and are therefore better for external use than simpler salicylates

The aryl esters (phenyl salicylate type) hydrolyze to active phenols and salicylic acid They have been used for intestinal antiseptics but are of doubtful value

The Council believes the clinical needs for salicylic acid compounds are fully met by the following official compounds no longer eligible for inclusion in *New and Nonofficial Remedies* salicylic acid U S P methyl salicylate U S P (for topical use) acetylsalicylic acid U S P and sodium salicylate U S P (for oral use) Consideration will be given to nonofficial derivatives of salicylic acid only if these can be clearly shown to have a usefulness not provided by the better known official compounds

Anesthetics

GENERAL ANESTHETICS

General anesthetics are drugs which depress the central nervous system in a progressive manner. Moderate dosage of many of them reduces or abolishes the perception of pain (analgesia) before consciousness is lost. The various reflex mechanisms are likewise inhibited in an orderly progression more or less characteristic of each drug.

To be effective such drugs must enter the blood stream to be carried to the nervous system. Portals of entry are the lungs (inhalation); the gastro-intestinal tract (oral or rectal administration); or by direct intravenous injection. Certain agents may be given by any of the three routes (e.g. ether).

The physical signs by which the extent of effect of these drugs may be estimated are based largely upon the resulting changes in the sensitivity of various reflexes as the dose is increased. Thus, general anesthesia is divided into stages and planes such as are described in the textbooks. Some drugs formerly looked upon as hypnotics are now used in much larger doses as general anesthetics (e.g. barbiturates). There can be no sharp delineation between hypnotics, sedatives and general anesthetics since effects are dependent upon the size of the dose as well as upon the pharmacological characteristics of the drug. For this reason, so-called basal anesthetics are described along with the general anesthetics.

CYCLOPROPANE-U. S. P.—Cyclopropanum—Trimethylene—"Contains not less than 99 per cent by volume of C_3H_6 "—U. S. P. The structural formula may be represented as follows:



For description and standards see the U. S. Pharmacopeia under Cyclopropane.

Actions and Uses.—Cyclopropane differs from other gaseous anesthetic agents in that the anesthetic-oxygen ratio is reversed—15 per cent of cyclopropane to 85 per cent of oxygen up to the rarely and briefly used 40 per cent of cyclopropane and 60 per cent oxygen. The high anesthetic potency of cyclopropane

as compared with other hydrocarbons makes its use advantageous from the standpoint that abundant concentrations of oxygen may be used. There is evidence to indicate that the rate of diffusion of cyclopropane is about twice that of ethylene. Cyclopropane is eliminated less rapidly than ethylene but much faster than ether. Induction and recovery with cyclopropane are therefore slower than with ethylene but more rapid than with ether.

There is some evidence to indicate that cyclopropane affects the autonomic tissue of the heart more than ether or chloroform. In high concentrations it heightens the irritability of this tissue and predisposes to the occurrence of cardiac arrhythmias. This effect has been shown to be enhanced with the simultaneous use of epinephrine. For these reasons the pulse must be carefully observed and the use of sympathomimetic drugs avoided during cyclopropane anesthesia. Cyclopropane does not stimulate respiration as do many other general anesthetic agents and for this reason preoperative sedation with respiratory depressants must be used with caution. The signs of Guedel for other anesthetic agents do not apply to cyclopropane so that familiarity with the signs of the stages of anesthesia for cyclopropane is absolutely essential in the administration of this agent.

The explosibility of cyclopropane oxygen mixtures is greater than that of other anesthetic oxygen mixtures because of the comparatively larger amounts of oxygen that are compatible with cyclopropane anesthesia. Any inert gas such as helium should be added to decrease the explosive hazard inherent with high oxygen concentrations. Careful operating room technique to avoid conditions conducive to the production of electrostatic sparks and the presence of open flames and the cautery should be observed with the same precautions as those for other explosive or inflammable anesthetics.

The advantages of cyclopropane consist in its effectiveness in concentrations providing an adequate supply of oxygen, less pulmonary irritation than ether (except in asthmatics), less excitement during induction and low toxicity. Its disadvantages include explosibility when oxygen rich mixtures are employed, lack of respiratory stimulation, difficulty in detection of the planes of anesthesia by those unfamiliar in its administration, occasional laryngospasm and tendency to produce cardiac arrhythmias and postanesthetic headache.

Dosage—Cyclopropane is usually furnished in compressed form in metal containers. In use the gas is passed into an inhalation apparatus of the closed circuit type and is then administered by inhalation from a rebreathing bag always with the admixture of oxygen. The concentration employed varies from 15 to 40 per cent and with the individual patient but should probably not exceed 30 per cent. The remainder of the mixture should consist of a minimum of 20 per cent oxygen, but this should be supplied in quantities adequate for physio-

LOCAL ANESTHETICS

Local anesthesia (that confined to a restricted area or part) may be produced in a variety of ways according to the site of application and the method or technic of administration. Topical designated as surface anesthesia, tetracaine) are effective (ne) are less satisfactory for reduce freezing temperature (chloride, carbon dioxide snow) and protoplasmic poisons (phenol) are rarely used at present.

Local anesthesia produced by injectable compounds is designated according to the technic or anatomical site chosen: as infiltration (injection directly into the area which is painful or subjected to surgical trauma), or block (injection in proximity to specific nerve trunks supplying a particular anatomical site). Block injections are designated according to the point chosen for interruption of nerve transmission. Some of these are: spinal and ed im- bony spinal or caudal canals), and other innumerable blocks designated according to their anatomical location along the course of nerve trunks on their way to the peripheral tissues.

A special dosage form of local anesthetics may also be used to induce continuous caudal analgesia for use in obstetric cases, *provided the procedure is carried out with great care and caution and is undertaken only by skilled specialists. It is not a procedure for untrained hands.* (See caution under the general article, Local

stantly when the needle is being inserted

If a ureteral catheter is to be employed, entry into the caudal canal should be made with a needle no larger than 15 gauge. If it is necessary to use a needle as large as 13 gauge and the caudal canal is not entered on the first attempt, the method should be discarded; otherwise infection is almost certain to occur. Infection is one of the great dangers encountered in continuous caudal analgesia and extreme care must be exercised to prevent this condition. There should be at hand emergency measures to control untoward reactions. Soluble barbiturates (e.g. Hexobarbital Soluble N. N. R., Thiopental Sodium

U. S. P.) are useful to control convulsions should they occur. Oxygen should be immediately accessible.

Continuous caudal analgesia is contraindicated in the presence of placenta praevia, inertia uteri, uncontrollable hysteria, anomalies of the sacrum and disproportion of child and pelvis. It is not suitable for difficult forceps rotation or version, as in such cases complete relaxation of the uterus is imperative. History of sensitivity to local anesthetics is another contraindication.

The Council has recognized the use of local anesthetics to produce caudal analgesia, so that proper warnings may be issued.

(e.g. neosynephrine) is usually added in the preparation of solutions to impede and delay absorption. Concentration of such agents should be kept at a minimum. (See Sympathomimetic Agents in the chapter on Autonomic Drugs.)

To combat the vasodepressor effects of the local anesthetics, especially when injected more centrally (spinal or epidural) long acting vasoconstrictor agents (e.g. ephedrine) may be injected intramuscularly or intravenously for their systemic effect.

The technical details necessary to prepare and control solutions of drugs injected, especially within the subdural or epidural spaces, are intricate and exacting. These should be acquired from authoritative source books and from instruction by experienced anesthetists. Details of dosage of any of the several local anesthetics should be learned with reference to various modifications for different applications.

The toxicity of all local anesthetic agents is great and the tolerance of patients variable. There are certain limits of strength of solution and total dosage which must not be exceeded.

tion, rate and location of injection, along with age, emotional and physical status of the patient are a few of the factors in

to occur. Hence, when local anesthetic drugs are being used, it is in the interest of safety to have instantly available (a) oxygen and the means of inflating the lungs with it and (b) a quick act-

ing barbituric acid compound ready for intravenous administration.

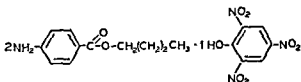
Slightly Soluble Local Anesthetics

The slight solubility of these anesthetics renders them unsuitable for injection, but the slow absorption renders them safer, especially for ulcers, wounds and mucous surfaces. The anesthesia which they induce is usually not so complete as that induced by the soluble local anesthetics; but it is more lasting. As a group they are practically nonirritant and nontoxic. Ethyl aminobenzoate (benzocaine, anesthesin) and orthoform are about equally effective through intact mucous membranes; butyl aminobenzoate (butesin) is claimed to be more effective than either.

They are used for painful wounds, ulcers, etc., of the skin and accessible mucous membranes; for instance, after dental operations.

Many, if not all, local anesthetics occasionally give rise to dermatitis. When this is severe, the use of the anesthetic should be discontinued.

BUTAMBEN PICRATE—Butesin Picrate (ABBOTT).—Di-*n*-butyl-*p*-aminobenzoate-trinitrophenol.—A compound consisting of one molecule of trinitrophenol (picric acid) and two molecules of the normal butyl ester of 4-aminobenzoic acid. The structural formula may be represented as follows:



For tests and standards, see Section B.

Actions and Uses.—An aqueous solution of 1 in 2,000 produces immediate and complete anesthesia of the eye which lasts from ten to twenty minutes. Butamben picrate is used in the treatment of burns, ulcers and other denuded painful lesions of the skin.

Instances of butamben picrate dermatitis have occurred which are probably due to idiosyncrasy. A development of a rash following the use of the drug is an indication for its discontinuance.

Dosage.—For use, a 1 per cent butamben picrate ointment is proposed.

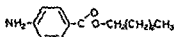
ABBOTT LABORATORIES

Ointment Butesin Picrate with Metaphen: Butamben picrate 1 per cent, and metaphen 1:5,000, incorporated in an ointment base composed of white wax, paraffin, petrolatum, sodium borate and water, 99 per cent.

Ophthalmic Ointment Butesin Picrate 1% and Butesin 1% Butamben picrate, 1 per cent, Butamben, 1 per cent and soft petrolatum, 98 per cent

U S. patent 1 596 259 (Aug. 17 1926 expired) U S trademark 175 093

BUTYL AMINO BENZOATE-U S P—Butesin (ABBOTT).—*n* Butyl *p* aminobenzoate The structural formula may be represented as follows



For description and standards see the U S Pharmacopeia under Butyl Aminobenzoate

Actions and Uses—See general article Slightly Soluble Local Anesthetics The actions and uses of butyl aminobenzoate are similar to those of ethyl aminobenzoate U S P but it is claimed to be more effective

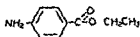
Dosage—Butyl aminobenzoate is used as a dusting powder either with or without a diluent It may be used in the form of troches ointment, or suppositories or dissolved in a fatty oil Its oil solutions may be sterilized by heat.

ABBOTT LABORATORIES

Butesin (Powder) Bulk

U S. patent 1 440 652 (Jan 2 1923 expired) U S trademark 175 095

ETHYL AMINO BENZOATE U S P—Anesthesin (ABBOTT)—Anaesthesin (WINTHROP-STEARNES)—Benzocaine Ethyl *p* aminobenzoate. The structural formula may be represented as follows



For description and standards see the U S Pharmacopeia under Ethyl Aminobenzoate and Ethyl Aminobenzoate Ointment.

Actions and Uses—See general article, Slightly Soluble Local Anesthetics

Dosage—Used as a dusting powder either with or without a diluent It may be applied in ointment or in the form of suppositories.

ABBOTT LABORATORIES

Anesthesin (Powder) Bulk.

U S trademark 55 744.

MERCK & CO., INC.

Benzocaine (*Powder*): Bulk.

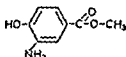
WINTHROP-STEARNs, INC.

Anaesthesin Jelly: 45 cc. collapsible tube.

Anaesthesin (*Powder*): Bulk.

U. S. trademark 55,744

ORTHOFORM. — Orthoform-New. — Methyl *m*-amino-*p*-hydroxybenzoate. The structural formula may be represented as follows:



For tests and standards, see Section B.

Actions and Uses—Orthoform is a local anesthetic, but penetrates the tissues very slowly on account of its insolubility. It has no action on the unbroken skin. It is practically non-toxic in the usual doses.

It has been applied locally as an analgesic to wounds of every description. It has been used in dentistry and in nasal catarrh, hay fever, etc.

Dosage.—The Council does not approve of the internal use of this drug. It is used with milk sugar for insulin pencilings, or with oil for

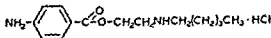
WINTHROP-STEARNs, INC.

Orthoform (*Powder*): 5 Gm. vials, and 31.1 Gm. bottles.

U. S. patents 610,348 (Sept. 6, 1898; expired), and 625,158 (May 16, 1899; expired)

Soluble Local Anesthetics

AMYLsINE HYDROCHLORIDE (Novocor). — 2-*p*-aminobenzoic acid, amylaminocarbonyl hydrochloride. (*Formel*



For tests and standards, see Section B

Actions and Uses—The actions of this compound resemble those of cocaine hydrochloride, but it does not cause mydriasis when the solution is dropped into the eye. In the present state of production mydriasis is not induced in all species and is induced promptly with little smarting, it does not increase intraocular tension.

Dosage.—A 2 per cent or 4 per cent solution is used in ophthalmology when mydriasis is not desired, 1 or 2 drops being usually sufficient.

NOVOCOL CHEMICAL MFG. CO., INC.

Amylsine Hydrochloride (Powder): 5 Gm. vials and 30 cc. bottles.

Solution Amylsine Hydrochloride 4%: 30 cc. bottles.

U S Patent 2,139,818 (Dec. 13, 1938, expires 1955). U S trademark 404,009

BENZYL ALCOHOL—N. F.—Phenylcarbinol—An aromatic alcohol occurring as an ester in tolu and other balsams; the product on the market is produced synthetically. The structural formula may be represented as follows



For description and standards see The National Formulary under Benzyl Alcohol

Actions and Uses—Benzyl alcohol is used as a local anesthetic by injection and by application to mucous membranes. It is practically nonirritant and nontoxic in the ordinary concentrations and doses. (See caution under the general article, Local Anesthetics)

Dosage.—Benzyl alcohol is usually used in the form of a 1 to 10 alcohol and water

SEYDEL CHEMICAL COMPANY

Benzyl Alcohol: Bulk.

BUTACAINE SULFATE—U. S. P.—Butyn Sulfate (Aspart)—3-(p-Aminobenzoxy)-1-di-n-butylaminopropane Sulfate. The structural formula may be represented as follows

solutions (1 in 2,000) cause slight temporary vascular dilatation (avoided by the addition of epinephrine solution 1 in 10,000) by () in amounts to exceed 20 cc. (approximately 12 mg.).

Dosage.—For infiltration anesthesia solutions of from 1 in 2,000 to 1 in 1,000, with the addition of 0.1 cc. of epinephrine hydrochloride solution (1 in 1,000) to 100 cc. of the solution. Not more than 100 cc. of 1 in 1,000 solution should be injected. For spinal anesthesia, a total of from 7.5 to 10 mg. in 1 in 1,500 solution which is made by diluting a 1 in 200 solution with an appropriate quantity of spinal fluid; for sacral anesthesia, 25 to 35 cc. of 1 in 1,000 solution or a correspondingly smaller volume of 1 in 500 solution. Aqueous solutions of dibucaine hydrochloride should be prepared with distilled water, as the salts present in tap water of many localities may precipitate the free base. Alkali-free glass should be used in the preparation of its solutions. (See caution under the general article, Local Anesthetics)

CIBA PHARMACEUTICAL PRODUCTS, INC

Solution Nupercaine Hydrochloride 1:200 (Buffered):
2 cc. ampuls.

Solution Nupercaine Hydrochloride 1:1,000: 5 cc. and
25 cc. ampuls.

Solution Nupercaine Hydrochloride 1:1,500 in 0.5%
Sodium Chloride: 20 cc. ampuls.

Solution Nupercaine Hydrochloride 1:1,000, with Epi-
nephrine, 1:100,000: 2 cc. and 5 cc. ampuls

Solution Nupercaine Hydrochloride 2%:

Tablets Nupercaine Hydrochloride: 50 mg.

U. S. patent 1,825,623. U. S. trademark 266,366

U. S. PATENT 1,825,623. U. S. TRADEMARK 266,366

For tests and standards, see Section B under Dipiperodon and
Oxyquinoline Benzoate.

Actions and Uses—See under Dipiperodon Hydrochloride.

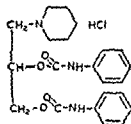
Dosage.—See under Dipiperodon Hydrochloride.

THE WM. S. MERRELL COMPANY

Diothane Ointment with Oxyquinoline Benzoate: Bulk.
28.4 Gm. tubes. Dipiperodon 1 per cent and oxyquinoline benzoate
0.1 per cent, in an ointment base consisting of petrolatum, lan-
oline and mineral oil.

U. S. patent 2,004,132 (June 11, 1935, expires 1952). U. S. trademark
296,850.

DIPERODON HYDROCHLORIDE—Diothane Hydrochloride (MERRELL)—The di Phenylurethane of 1 Pi peridinopropane 2,3 diol Hydrochloride—Diperodon hydrochloride is obtained by combining piperidine and glycerol monochlorohydrin in the presence of an alkali and reacting the piperidinopropaneidol with phenyl isocyanate. The structural formula may be represented as follows



For tests and standards see Section B

Actions and Uses—Nearly similar to those of cocaine but it is claimed that the anesthesia lasts somewhat longer than that induced by corresponding doses of cocaine hydrochloride or procaine hydrochloride. Its toxicity by intravenous injection is about three times that of procaine hydrochloride and hence it should not be injected except in small amounts. Diperodon hydrochloride is also available as a cream for topical use as a surface anesthetic and analgesic. It is claimed to be useful for the relief of surface pain and irritation in abrasions of the skin and mucous membranes, following hemorrhoidectomy and for the relief of pain in nonoperable cases of hemorrhoids.

Solutions of diperodon hydrochloride prepared extemporaneously should be used promptly since such solutions usually contain traces of alkali and are thereby subject to precipitation.

Dosage—A 1 per cent solution is applied to mucous membranes. 0.5 per cent solutions may be injected. (See caution under the general article Local Anesthetics.) The cream is rubbed into the affected area, a second thin coating applied, and covered with dressings within ten or fifteen minutes.

THE W. S. MERRELL COMPANY

Diothane Hydrochloride (Crystals) Bulk

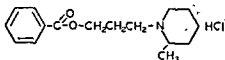
Diothane Hydrochloride (Cream) 30 Gm. tubes and 400 Gm. jars.

Solution Diothane Hydrochloride 0.5% with Sodium Chloride 0.6%, 6 cc ampuls

Solution Diothane Hydrochloride 1% A solution of Diperodon Hydrochloride, 1 per cent, in distilled water

U. S. patent 2,074,132 (June 11, 1935 expires 1952) U. S. trade mark 296,850

PIPEROCAINE HYDROCHLORIDE — Metycaine Hydrochloride (LILLY). — 3-Benzoxo-1-(2-methylpiperidino) propane Hydrochloride. The structural formula may be represented as follows:



For tests and standards, see Section B

Actions and Uses.—Piperocaine hydrochloride is a local anes-

toxicity following subcutaneous injection is lower than that of cocaine and comparable to that of procaine; intravenously, it was found to be approximately three times as toxic as procaine. It is considered the approximate equivalent of procaine for spinal anesthesia.

Dosage.—For application to the eye piperocaine hydrochloride is used in 2 to 4 per cent solutions; for nose and throat, 2 to 10 per cent; for the urethra, 1 to 4 per cent; for infiltrative anesthesia, 0.5 to 1 per cent; for nerve block, 1 to 2 per cent; for spinal anesthesia, 1.5 to 5 per cent with a maximum quantity of drug of 0.75 mg. per pound of body weight to an absolute maximum of 150 mg. (See caution under the general article, Local Anesthetics.)

ELI LILLY AND COMPANY

Metycaine Hydrochloride (Powder): 15 Gm. and 120 Gm. bottles

Ointment Metycaine Hydrochloride 5%: Piperocaine hydrochloride 5 per cent in a base consisting of white petrolatum with white wax and wool fat.

Ophthalmic Ointment Metycaine Hydrochloride 4%: Piperocaine Hydrochloride 4 per cent, in a base consisting of liquid petrolatum, wool fat and with small amounts of paraffin, white petrolatum and ceresin

Solution Metycaine Hydrochloride 1.5%: 200 cc ampul-bottles. Each cubic centimeter contains 15 mg. of piperocaine hydrochloride in Ringer's solution. For caudal anesthesia.

Solution Metycaine Hydrochloride 2%: 30 cc. bottles. Piperocaine hydrochloride 2 per cent in Ringer's solution. Preserved with chlorbutanol 0.5 per cent.

Solution Metycaine Hydrochloride 20%: 5 cc. ampuls. Each 5 cc. contains piperocaine hydrochloride 1 Gm. in distilled

water. To be used for infiltration and regional anesthesia. The solution must be diluted before using

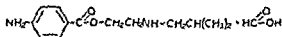
Solution Metycaine Hydrochloride in Ringer's Solution (For Spinal Anesthesia): 15 per cent, 5 cc. and 20 cc. ampuls; 2 per cent, 30 cc. vials, 5 per cent, 3 cc. ampuls

Tablets Metycaine Hydrochloride: 0.15 Gm

U S patent 1,784,903 (Dec. 16, 1930, expires 1947). U S trademark 305,894

BUTETHAMINE FORMATE—Monocaine Formate
 p aminobenzoate formate.—
 formed from p aminobenzoic
 of ethanalamine. The struc-

tural formula may be represented as follows



For tests and standards, see Section B

detour and then Butethamine formate is prepared for use

Because of the use of other agents for spinal anesthesia

formate should correspond to about three-fourths of that ordinarily employed for procaine

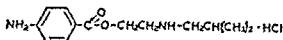
NOVOCOL CHEMICAL MFG CO, INC.

Monocaine Formate (Crystals): 50, 100, 150 and 200 mg ampuls, 300 and 500 mg containers (fractional doses). For spinal anesthesia.

Solution Monocaine Formate 5%: 2 cc. ampuls for spinal anesthesia. Each cubic centimeter contains 50 mg of butethamine formate in sterile distilled water

U S. patent 2,139,818 (Dec 13, 1933 expires 1955) U S trademark 352,633

BUTETHAMINE HYDROCHLORIDE—Monocaine
 HCl hydrochloride (5% aqueous solution) contains 50 mg of butethamine



For tests and standards, see Section B.

Actions and Uses.—Butethamine hydrochloride is a local anesthetic similar to procaine hydrochloride. It is used for nerve block anesthesia in dentistry or other surgical operations. Present evidence does not warrant recommendation for its use for topical or surface anesthesia of mucous or other membranes. Its effects, either with or without the addition of epinephrine hydrochloride, are qualitatively identical in every respect with those of procaine. Quantitatively, monocaine has been shown to have about one-third more anesthetic and toxic potency than procaine (i. e., monocaine solutions of three-fourths the concentration of procaine solutions are approximately equivalent).

Dosage.—For dental or other minor surgery, a 1 per cent solution with epinephrine 1:75,000 may be injected to obtain nerve block anesthesia. In major surgery or other procedures requiring nerve block anesthesia equivalent to that produced by 2 per cent procaine, a 1.5 per cent solution of butethamine with epinephrine 1:100,000 may be used. (See caution under the general article Local Anesthetics.)

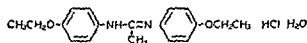
NOVOCOL CHEMICAL MFG CO., INC.

Solution Monocaine Hydrochloride 1% with Epinephrine 1:75,000: 2 cc., 3 cc. and 5 cc. ampuls; 2 cc., 2.5 cc. and 5 cc. Anestubes (syringe cartridge); 2.5 cc. and 5 cc. Novompuls (ampul type syringe); and 30 cc., 60 cc. and 120 cc. bottles. Each cubic centimeter contains butethamine hydrochloride 10 mg., epinephrine U. S. P. 0.013 mg., sodium bisulfite 2.0 mg. and sodium chloride 6.5 mg. in sterile distilled water.

Solution Monocaine Hydrochloride 1.5% with Epinephrine 1:100,000: 2 cc., 3 cc. and 5 cc. ampuls, 1 cc., 2 cc., 2.5 cc. and 5 cc. Anestubes (syringe cartridge); 2.5 cc. and 5 cc. Novompuls (ampul type syringe); 60 cc. and 120 cc. bottles. Each cubic centimeter contains butethamine hydrochloride 15 mg., epinephrine U. S. P. 0.01 mg., sodium bisulfite 2.0 mg. and sodium chloride 4.5 mg. in sterile distilled water.

U. S. patent 2,139,818 (Dec. 13, 1938, expires 1955). U. S. trademark 353,653.

PHENACAINE HYDROCHLORIDE—U. S. P.—Holo-caine Hydrochloride (WINTHROP-STEARN).—bis-*p*-Ethoxy-phenylacetamidine hydrochloride monohydrate—"When dried at 105° C. for 6 hours, contains not less than 87.5 per cent and not more than 90.5 per cent of phenacaine base ($\text{C}_{18}\text{H}_{22}\text{N}_2\text{O}_2$), corresponding to not less than 98 per cent of $\text{C}_{18}\text{H}_{22}\text{N}_2\text{O}_2 \cdot \text{HCl}$." U. S. P. The structural formula may be represented as follows:



For description and standards see the U S Pharmacopeia under Phenacaine Hydrochloride.

Actions and Uses—Phenacaine hydrochloride is a local anesthetic like cocaine but having the advantage of a quicker effect. A quarter of a cubic centimeter of a 1 per cent solution when instilled into the eye is usually sufficient to cause anesthesia in from one to ten minutes. This is preceded by temporary smarting.

Dosage—It is applied in a 1 per cent aqueous solution.

are not injured by boiling

MANHATTAN EYE SALVE COMPANY INC

Ointment Holocaine 1% Collapsible ophthalmic tubes
Phenacaine hydrochloride 1 per cent water 1 per cent wool fat, 5 per cent and petrolatum sterile 93 per cent

Ointment Holocaine and Adrenalin Collapsible ophthalmic tubes. Composed of phenacaine hydrochloride 1 per cent adrenalin chloride solution, 2 per cent water 1 per cent wool fat 10 per cent white petrolatum sterile 86 per cent

WERNER DRUG & CHEMICAL CO

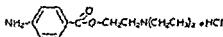
Phenacaine Hydrochloride (Powder) Bulk and 1 Gm 5 Gm 30 Gm 125 Gm and 500 Gm packages

WINTHROP STEARNS INC.

Holocaine Hydrochloride (Powder) Bulk

U S trademark 32,210 (Chemical Foundation Inc.)

PROCAINE HYDROCHLORIDE U S P.—Novocain (WINTHROP-STEARNES)— β diethylaminoethyl p aminobenzoate hydrochloride. The structural formula may be represented as follows



For description and standards see the U S Pharmacopeia under Procaine Hydrochloride and The National Formulary under Procaine Hydrochloride Ampuls Procaine Hydrochloride Solution and Procaine Hydrochloride Tablets

Actions and Uses—Procaine hydrochloride is a local anesthetic, a cocaine substitute. It is a prompt and powerful anesthetic. This may be compared with epinephrine. Procaine

It is relatively ineffective when applied to intact mucous membranes. It is probably the safest agent employed for spinal anesthesia. A special dosage form of procaine hydrochloride may also be used to induce continuous caudal analgesia for use in obstetric cases, *provided the procedure is carried out with great care and caution and is undertaken only by skilled specialists. It is not a procedure for untrained hands.* (See caution under the general article, Local Anesthetics.)

Dosage.—For infiltration anesthesia, solutions of 0.25 Gm. procaine hydrochloride in 50 or 100 cc. isotonic solution of sodium chloride, with 0.3 or 0.6 cc. of epinephrine hydrochloride solution (1 in 1,000) for instillations and injections, solutions of 0.1 Gm. procaine hydrochloride in 5 or 10 cc. isotonic solution of sodium chloride, with 0.3 or 0.6 cc. of epinephrine hydrochloride solution (1 in 1,000) for instillations and injections. Even up to 10 per cent solutions are used. 4 to 0.5 cc. of epinephrine solution to each 10 cc. For spinal anesthesia concentrations of 5 per cent or less are considered safe; the total amount injected at one time should not exceed 200 mg. of the drug.

ABBOTT LABORATORIES

Procaine Hydrochloride (Crystals): Bulk.

Procaine Hydrochloride for Spinal Anesthesia (Crystals): 50 mg., 100 mg., 120 mg., 150 mg., 200 mg. and 500 mg ampuls.

Solution Procaine Hydrochloride 1%: 1.5 cc. ampuls. Each ampul contains procaine hydrochloride 15 mg. in chemically pure water with sodium chloride sufficient to make an isotonic solution.

Solution Procaine Hydrochloride 1%: 100 cc. bottle. Each cc. contains procaine hydrochloride 10 mg., sodium chloride 6 mg., sodium bisulfite 1 mg. and distilled water.

Solution Procaine Hydrochloride 1.5%: 250 cc. bottles. Each 100 cubic centimeters contains procaine hydrochloride 1.5 Gm.

Solution Procaine Hydrochloride 2%: 1 cc. and 5 cc. ampuls. Each cc. contains procaine hydrochloride 20 mg. and sodium chloride 5 mg. in distilled water to make an isotonic solution.

Solution Procaine Hydrochloride 2% 100 cc vials Each cc. contains procaine hydrochloride 20 mg sodium chloride 44 mg sodium bisulfite 1 mg in sterile distilled water

Solution Procaine Hydrochloride 5% 10 cc ampuls Each 10 cc. contains procaine hydrochloride 0.5 Gm. in water with 0.1 per cent sodium thiosulfate

Solution Procaine Hydrochloride 20% 5 cc. ampuls Each 5 cc. contains procaine hydrochloride 1 Gm in water with 0.1 per cent sodium thiosulfate.

Solution Procaine Hydrochloride 10% for Spinal Anesthesia 2 cc. ampuls Each cc. contains procaine hydrochloride 0.1 Gm in distilled water

Solution Procaine Hydrochloride 2% with Epinephrine Hydrochloride 1:25,000 1 cc ampuls Each cc. contains procaine hydrochloride 20 mg epinephrine hydrochloride 0.04 mg sodium bisulfite 1 mg and potassium sulfate 9 mg in distilled water to make an isotonic solution

Solution Procaine 2%	with Epinephrine
	Each cc contains
	hydrochloride 0.04
	sulfate 9 mg in dis

Tablets Procaine Hydrochloride 70 mg 0.15 Gm. and 0.2 Gm One tablet dissolved in 4 cc. 8 cc or 10 cc of distilled water respectively makes a 2 per cent solution of procaine hydrochloride

Hypodermic Tablets Procaine Hydrochloride 20 mg

Hypodermic Tablets Procaine Hydrochloride 20 mg with Epinephrine Hydrochloride 1:25,000 Each contains procaine hydrochloride 20 mg epinephrine hydrochloride 0.04 mg and sodium chloride sufficient so that when the tablet is dissolved in 1 cc of water the resulting solution is approximately isotonic and contains 2 per cent procaine hydrochloride and 1:25,000 epinephrine hydrochloride

BARRY BIOLOGICAL LABORATORY DIVISION OF BARRY LABORATORIES INC.

Solution Procaine Hydrochloride 2% 30 cc bottles Each cc. contains procaine hydrochloride 20 mg sodium chloride 44 mg sodium bisulfite 1.0 mg Preserved with chlorobutanol 0.5 per cent

Solution Procaine Hydrochloride 2% with Epinephrine Hydrochloride 1:25,000 30 cc bottles Each cc. contains procaine hydrochloride 20 mg epinephrine hydrochloride 0.04 mg and sodium chloride in distilled water to make an isotonic solution with sodium bisulfite 1 mg Preserved with chlorobutanol 0.5 per cent

GEORGE A. BREON & COMPANY

Solution Procaine Hydrochloride 2%: 30 cc. vials Each cc. contains 20 mg. procaine hydrochloride in isotonic solution of sodium chloride. Preserved with chlorobutanol 0.5 per cent.

BREWER & Co., INC.

Solution Procaine Hydrochloride 2% with Epinephrine Hydrochloride 1:25,000: 30 cc. vials Each cc. contains procaine hydrochloride 20 mg., epinephrine hydrochloride 0.04 mg. and sodium chloride 3.7 mg. in water, with sodium bisulfite 0.1 per cent. Preserved with chlorobutanol 0.5 per cent.

BRISTOL LABORATORIES, INC.

Solution Procaine Hydrochloride 2%: 1 cc. ampuls. Each cc. contains 20 mg. procaine hydrochloride, chlorobutanol 5 mg. in isotonic solution of sodium chloride.

Solution Procaine Hydrochloride 1% with Epinephrine Hydrochloride 1:25,000: 3 cc. ampuls. Each cc. contains procaine hydrochloride 10 mg. epinephrine hydrochloride 0.04 mg., chlorobutanol 5 mg. and sodium bisulfite 1 mg. in isotonic solution of sodium chloride

ENDO PRODUCTS, INC.

Solution Procaine Hydrochloride 2%: 2 cc. ampuls. Each cc. contains 20 mg. of procaine hydrochloride, 5 mg. of chlorobutanol and 1 mg. of sodium bisulfite in distilled water.

Solution Procaine Hydrochloride 2%: 30 cc. and 100 cc. vials. Each cc. contains 20 mg. procaine hydrochloride, 5 mg. of chlorobutanol and 1 mg. of sodium bisulfite in distilled water.

Solution Procaine Hydrochloride 2% with Epinephrine Hydrochloride 1:25,000: 30 cc. and 100 cc. vials. Each cc. contains 20 mg. of procaine hydrochloride, 0.04 mg. of epinephrine hydrochloride, 5 mg. of chlorobutanol and 1 mg. of sodium bisulfite in distilled water.

LAKESIDE LABORATORIES, INC.

Procaine Hydrochloride 2%: 30 cc. and 100 cc. vials. Each cc. contains procaine hydrochloride 20 mg., sodium bisulfite 1 mg. and chlorobutanol 5 mg. in isotonic sodium chloride solution.

LINCOLN LABORATORIES, INC.

Solution Procaine Hydrochloride 2%: 100 cc vials Each cc. contains procaine hydrochloride 2 per cent in distilled water. Preserved with chlorobutanol 0.5 per cent.

MERCK & Co., INC

Procaine Hydrochloride (Crystals): Bulk.

THE WM S MERRELL CO.

Solution Procaine Hydrochloride 1%: 1 cc and 10 cc. ampuls Each cc. contains procaine hydrochloride 10 mg in isotonic solution of sodium chloride

Solution Procaine Hydrochloride 1%: 30 cc and 100 cc Each cc. contains procaine hydrochloride 10 mg in isotonic solution of sodium chloride Preserved with chlorobutanol 0.5 per cent

Solution Procaine Hydrochloride 2%: 30 cc and 100 cc Each cc. contains procaine hydrochloride 20 mg in isotonic solution of sodium chloride Preserved with chlorobutanol 0.5 per cent

Solution Procaine Hydrochloride 2%: 1 cc and 10 cc ampuls Each cc contains procaine hydrochloride 20 mg in isotonic solution of sodium chloride 40 cc and 160 cc bottles

E S MILLER LABORATORIES, INC

Solution Procaine Hydrochloride 1%: 30 cc., 50 cc. and 100 cc vials and 2 cc and 5 cc ampuls. Preserved with chlorobutanol 0.5 per cent

Solution Procaine Hydrochloride 2%: 30 cc.; 50 cc. and 100 cc vials and 2 cc and 5 cc. ampuls Vials preserved with 0.5 per cent chlorobutanol.

E. R. SQUIBB & SONS

Procaine Hydrochloride for Spinal Anesthesia (Crystals): 50 mg, 100 mg, 120 mg, 150 mg, 200 mg, 500 mg ampuls and 100 Gm. bottles

THE UPJOHN COMPANY

Solution Procaine Hydrochloride 1%: 30 cc and 100 cc vials Each cc contains procaine hydrochloride 10 mg in isotonic solution of sodium chloride Preserved with chlorobutanol 0.4 mg

Solution Procaine Hydrochloride 2%: 30 cc and 100 cc vials Each cc contains procaine hydrochloride 20 mg in isotonic solution of sodium chloride Preserved with chlorobutanol 0.4 mg

saturated with carbon dioxide

Solution Procaine Hydrochloride 2% with Epinephrine Hydrochloride 1:20,000. 30 cc vials Each cc contains procaine hydrochloride 20 mg., epinephrine hydrochloride 0.05 mg., sodium bisulfite 26 mg., benzoic acid 0.3 mg., sodium chloride

83 mg., normal hydrochloric acid 0.0016 cc. and chlorobutanol not to exceed 5 mg. in distilled water saturated with carbon dioxide.

Hypodermic Tablets Procaine Hydrochloride 20 mg. with Epinephrine Hydrochloride 1:40,000: Each contains procaine hydrochloride 20 mg., epinephrine hydrochloride 0.025

U. S. STANDARD PRODUCTS CO.

Solution Procaine Hydrochloride 2% with Epinephrine Hydrochloride 1:25,000: 1 cc. ampuls. Each cc. contains procaine hydrochloride 20 mg., epinephrine hydrochloride 0.04 mg. and sodium bisulfite 0.45 mg. in distilled water.

WINTHROP-STEARNs, INC.

Novocain (*Crystals*): Bulk.

Novocain for Spinal Anesthesia (*Crystals*): 50 mg., 100 mg., 120 mg., 150 mg., 200 mg., 300 mg. and 500 mg. ampuls.

Solution Novocain 1%: 2 cc. and 6 cc. ampuls. Each cc. contains procaine hydrochloride 10 mg., sodium chloride 6 mg. and sodium bisulfite not more than 1 mg. in distilled water.

Solution Novocain 2%: 3 cc. ampuls. Each cc. contains procaine hydrochloride 20 mg., sodium chloride 4 mg. and sodium bisulfite not more than 1 mg. in distilled water.

Solution Novocain 2%: 30 cc. bottles. Each cc. contains procaine hydrochloride 20 mg., sodium chloride 3.5 mg., sodium bisulfite 2 mg. and chlorobutanol 2.5 mg. as a preservative.

Solution Novocain 10% for Spinal Anesthesia: 2 cc. ampuls. Each cc. contains procaine hydrochloride 0.1 Gm. and acetone sodium bisulfite not more than 4 mg. in distilled water.

Solution Novocain 20%: 1.5 cc. and 5 cc. ampuls. Each cc. contains procaine hydrochloride 0.2 Gm. and sodium bisulfite not more than 5 mg. in distilled water. This solution must be diluted before use.

Solution Novocain 1% with Suprarenin Bitartrate 1:100,000: 30 cc. bottles. Each cc. contains procaine hydrochloride 10 mg., epinephrine bitartrate 0.01 mg., sodium chloride 4 mg., potassium sulfate 4 mg., sodium bisulfite not more than 2.5 mg. and chlorobutanol 2.5 mg.

Solution Novocain 1% with Ephedrine Hydrochloride 5%: 1 cc. and 2 cc. ampuls. Each cc. contains procaine hydro-

thetia, for which purpose the dose is from 2 to 4 cc. (containing from 10 to 20 mg. of the salt). A total of 20 mg. is considered the maximum safe dose for spinal injection.

For continuous caudal analgesia the appropriate dosage form of tetracaine hydrochloride is made up for 0.15 per cent solution, e. g. 4 cc. sterile isotonic saline solution to 250 mg. and diluted further with sterile isotonic saline solution to a volume of 100 cc. An initial skin wheal is raised with the local anesthetic and the underlying tissues infiltrated so that the needle to be inserted into the sacral canal may be inserted without too much discomfort by the patient. Thirty cc. tetracaine hydrochloride 0.15 per cent solution is injected. Signs of fullness in one or both lower progressive loss of painful sensations and uterine cramps will be relieved.

analgesic solutions depend on the concentration of tetracaine. Intervals of 40 to 90 minutes are sufficient to keep the patient comfortable during the entire course of labor. In many cases approximately 100 cc. of the 0.15 per cent solution would be sufficient for the management of labor and delivery and repairs.

WINTHROP-STEARN, INC.

Pontocaine Hydrochloride "Niphanoid" for Spinal Anesthesia 10 mg. and 20 mg. Ampuls containing tetracaine hydrochloride in finely divided and instantly soluble form. The trade term "Niphanoid" (from the Greek "snow like") is applied to the process whereby dilute solutions of the drug are subjected to rapid freezing and subsequent evaporation of the solvent under high vacuum, the resultant material is claimed to be more readily soluble.

Ophthalmic Ointment Pontocaine Base An ointment containing 0.5 per cent of tetracaine base, the free base of tetracaine hydrochloride, dissolved in white petrolatum.

Solution Pontocaine Hydrochloride 1% 2 cc. ampula. Each 2 cc. of solution contains tetracaine hydrochloride 20 mg., sodium chloride 13.3 mg., and acetone bisulfite 4 mg.

Solution Pontocaine Hydrochloride 0.5% 15 cc. bottles. Preserved with chlorobutanol 0.4 per cent.

Solution Pontocaine Hydrochloride 2% 30 cc. and 120 cc. bottles. The solution contains 0.4 per cent chlorobutanol as a preservative and is tinted with methylene blue to prevent accidental use for injection.

Tablets Pontocaine Hydrochloride 0.1 Gm. Each tablet contains tetracaine hydrochloride 0.1 Gm., boric acid 5 mg., acetone sodium bisulfite not more than 0.5 mg. To be used only for preparing solutions for surface anesthesia (not for injection) in rhinolaryngology, ophthalmology and dentistry.

U. S. Patent 1,837,641 (Nov. 27, 1931; expires 1941) U. S. trade mark 252,416.

drochloride 60 mg., synthetic epinephrine as bitartrate 0.06 mg., boric acid 3.39 mg. and acetone sodium bisulfite not more than 1.29 mg.

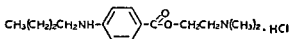
Hypodermic Tablets Novocain 80 mg. with Synthetic 1-Suprarenin Bitartrate 0.06 mg. Each contains procaine hydrochloride 80 mg., synthetic epinephrine as bitartrate 0.06 mg., boric acid 3.19 mg. and acetone sodium bisulfite not more than 1.7 mg.

Hypodermic Tablets Novocain 0.1 Gm. with Synthetic 1-Suprarenin Bitartrate 0.25 mg. Each contains procaine hydrochloride 0.1 Gm., synthetic epinephrine as bitartrate 0.25 mg., boric acid 5.38 mg. and acetone sodium bisulfite not more than 2.16 mg.

Hypodermic Tablets Novocain 0.125 Gm. with Synthetic 1-Suprarenin Bitartrate 0.13 mg. Each contains procaine hydrochloride 0.125 Gm., synthetic epinephrine as bitartrate 0.13 mg., boric acid 4.13 mg. and acetone sodium bisulfite not more than 2.64 mg.

U. S. patent 812,554 (Feb. 13, 1906 expired). U. S. trademark 53,072.

The base of tetracaine hydrochloride belongs to the procaine type. It differs from procaine base in that one of the hydrogens of the *para*-amino group is replaced by a butyl group, and the two ethyl groups of procaine are replaced by two methyl groups in tetracaine base. The structural formula may be represented as follows:



For description and standards see the U. S. Pharmacopeia under Tetracaine Hydrochloride.

Actions and Uses.—Tetracaine hydrochloride is a local anesthetic with actions similar to those of procaine hydrochloride, but it is effective when applied to mucous membranes in lower concentrations. (See caution under the general article, Local Anesthetics.) It is used for surface anesthesia in the eye, nose and throat, and in spinal anesthesia in which the anesthesia is prolonged.

Dosage.—Solution of tetracaine hydrochloride, 0.5 per cent is used in the eye; a 2 per cent solution is applied to the nose and throat. A 0.5 per cent solution is injected for spinal anes-

thetia, for which purpose the dose is from 2 to 4 cc. (containing from 10 to 20 mg. of the salt). A total of 20 mg. is considered the maximum safe dose for spinal injection.

For continuous caudal analgesia the appropriate dosage form of tetracaine hydrochloride is made up for 0.15 per cent solution.

progressive loss of painful sensations and relief of abdominal

intervals of from 40 to 50 minutes are sufficient to keep the patient comfortable during the entire course of labor. In many cases approximately 100 cc. of the 0.15 per cent solution would be sufficient for the management of labor and delivery and repairs.

WINTHROP-STEARNs, INC.

"Niphanoid" for Spinal Anesthesia: Ampuls containing tetracaine in instantly soluble form. The Greek "snow like") is applied to the process whereby dilute solutions of the drug are subjected to rapid freezing and subsequent evaporation of the solvent under high vacuum, the resultant material is claimed to be more readily soluble.

Ophthalmic Ointment Pontocaine Base: An ointment containing 0.5 per cent of tetracaine base, the free base of tetracaine hydrochloride, dissolved in white petrolatum.

Solution Pontocaine Hydrochloride 1%: 2 cc. ampuls. Each 2 cc. of solution contains tetracaine hydrochloride 20 mg., sodium chloride 13.3 mg., and acetone bisulfite 4 mg.

Solution Pontocaine Hydrochloride 0.5%: 15 cc. bottles. Preserved with chlorobutanol 0.4 per cent.

Solution Pontocaine Hydrochloride 2%: 30 cc. and 120 cc. bottles. The solution contains 0.4 per cent chlorobutanol as a preservative and is tinted with methylene blue to prevent accidental use for injection.

Tablets Pontocaine Hydrochloride: 0.1 Gm. Each tablet contains tetracaine hydrochloride 0.1 Gm., boric acid 5 mg., acetone per am bisulfite not more than 0.5 mg. To be used only for preparing solutions for surface anesthesia (not for injection) in otolaryngology, ophthalmology and dentistry.

U. S. Patent 2,219,445 (Nov. 20, 1917, expires 1949) U. S. Trade Mark 322,618

Local Anti-Infectives

Drugs which are chiefly employed for their local effect as antibacterials, fungicides and antiprotozoan agents are included in this chapter. Certain agents of this class that are administered internally, either orally or parentally, though employed for their local action, are described in Chapter 5, Systemic Anti-Infectives.

organisms.

If it were possible to develop the ideal disinfectant, it would possess the following assets: high coefficient of disinfection, stability, solubility, penetrability, even in the presence of organic matter, nontoxicity, and noncorrosive and nonbleaching power. An ideal antiseptic would effect a marked bacteriostatic action and likewise would be stable, highly soluble, penetrable, nontoxic, noncorrosive and nonbleaching. Antiseptics and disinfectants should possess a nonspecific action on micro-organisms.

Criteria for the evaluation of disinfectants and antiseptics are

both
bac-
terially
active.
com-
pounds included in antibacterial agents have not yet been discovered

Pending the promulgation of standard criteria for the evaluation of disinfectants and antiseptics, the Council deems it advisable to recommend:

1. Phenol coefficients or other *in vitro* tests in the absence and in the presence of serum, using both vegetative bacterial cells and clostridial spores, with suitable recovery mediums containing, if known, neutralizing substances for the disinfectant being tested.

2. Data on germicidal efficiency under conditions simulating actual use by the method of Price (Price, P. B.: *The Bacteri-*

ology of Normal Skin A New Quantitative Test Applied to a Study of the Bacterial Flora and the Disinfectant Action of Mechanical Cleaning *J Infect Dis* 63 301 [Nov Dec.] 1938, Ethyl Alcohol as a Germicide, *Arch Surg* 38 528 [March] 1939) or better still by an extension of the method of Price (Bernstein L. H. T. Standardization of Skin Disinfectants

Memorandum, p 31)

3. Data on germicidal efficiency by an animal method such for example as suggested by Alice H Kempf and W J Nungester (An In Vivo Test for the Evaluation of Skin Disinfectants *ibid*, p 49) or R W Sarber (*ibid* p 50)

4 Evidence from animal experiments regarding irritant action on skin and mucosae and regarding systemic toxicity

5 Critical clinical evidence supporting claims of harmlessness and efficacy

6. Data on the bacteriostatic activity as distinguished from the germicidal activity of the disinfectant.

discussed as a Council re
[128 805-811 (July 14)]
are recommended by the

1 In Vitro Tests of Fungicide—The phenol coefficient test for disinfectants and antiseptics as modified by the American Public Health Association subcommittee should be used. For

(a) The test fungus should be *Trichophyton interdigitale* A

(b) Spore suspensions of this test fungus should be prepared from ten day agar cultures in a concentration of 5 million conidia per cubic centimeter For performing the test 0.5 cc. of this suspension is added to 5 cc. of the fungicide concentration being tested.

(c) ten mu
medium
chemical
trial for the rapid dissipation of the fungicide carried over In the case of fungicides exerting a strong fungistatic effect, subcultures must be made.

(d) The so-called "*Trichophyton rosaceum*" should not be used as a test species. It is less resistant than *Trichophyton* when tested by the method outlined here, although it often appears to be more resistant in plate tests.

The test procedures follow the plan outlined in United States Department of Agriculture Circular 198 for the determination of phenol coefficients.

2. Clinical Tests and Their Evaluation.—This involves the use of prepared preliminary outlines and of a protocol for each patient.

(a) Selection and Grading of Patients: The number of patients should be sufficiently large to permit their division into a test group and a control group. Each of these, in turn, should be large enough to permit results that will be significant when later divided into subgroups for purposes of analysis. In consultation, a group of dermatologists has estimated 50 as the minimum number for both the test and the control group. Bed patients are not suitable, because dermatophytosis sometimes disappears spontaneously with bed rest.

Each of the two groups should contain an equitable representation of mild, moderate and severe cases. It is advantageous to indicate on a diagram on the protocol just what the extent and type of lesion are for each patient.

(b) The Environment: This and other circumstances should be comparable in the two groups. The groups should be tested simultaneously. Thus results from group A which were secured in winter would not be comparable to ones secured on group B in the summer; dermatophytosis is worse in the summer. Similarly, results should be checked with age groupings in the two test groups lest they have too much of a disturbing influence in the evaluations. Youths are far more predisposed than the aged.

(c) Laboratory Diagnosis. As a check against the clinical diagnosis, scrapings should be examined under the microscope for the presence of fungus and also cultured at the beginning of the studies. These examinations should be regarded as only supplementary to the clinical findings; many cases of valid dermatophytosis fail to yield confirmatory laboratory evidence, but the laboratory examinations may clarify doubtful clinical cases, and a knowledge of the identity of the species may be valuable when analyzing therapeutic results later.

Thus a fungicide might be eventually discovered which was efficacious against *Trichophyton purpureum* or other fungus but not against other species, and vice versa.

(d) Number and Duration of Treatments: As a working rule, applications should be made night and morning for two weeks. A final or subfinal examination should be made at the end of four weeks.

(e) Faithfulness of Patient to Treatment: The investigator should appraise the human type of each patient before admitting

him to the test series and have no hesitance in rejecting the unpromising ones. Lapses in treatment demand that the patient be removed from the series and is one more reason for securing a larger number of patients at the beginning of the work than will be employed in the final evaluation.

(f) **Privacy on Part of Patients** Patients should be requested not to discuss their treatment programs with other patients, they may influence one another's opinions. For obvious reasons clinical tests should not be conducted on patients who are employed in plants which have a gainful interest in the fungicide being tested.

(g) **Local Irritant Effect of Fungicide** This should be substantially nil, considering the number of fairly effective therapeutic agents now existent which are free from irritant effects. Certainly the development of any reactions that are at all severe should at once condemn the agent.

(h) **Sensitization to the Fungicide** This factor enters into and is routinely inquired for in tests of local applications in general. In the case of dermatophytosis it will largely take care of itself during the clinical tests of fungicidal value, where the applications are 'interrupted' in the natural course of events. The appearance of flare ups shortly after the eighth day of treatment should be watched for. If they do appear a special set of tests for sensitization must be made.

(i) **Toxic Systemic Effects** These should not play a role of importance in the treatment. should be required whether the substance if so, the amount of tests can follow the infectants and anti- Bureau of Ships Circular 51D6 (Int.), Dec 15 1942, page 4 paragraph F—2d may be followed in this connection.

(j) **Readings of Results of Treatment** These should be made without any knowledge of the identity of the patient or of the treatment that has been employed. an assistant should have removed, if possible, any traces of telltale fungicide that may remain. Only in this way can the factor of bias be completely removed and a fair impartial evaluation secured. If at all possible, the readings should be made by a disinterested person.

(k) **Mycologic Checks on Therapeutic Results** These will have value only of a kind supplementary to the clinical opinions because of the increased difficulty in laboratory demonstration of fungi in treated lesions. At the conclusion of therapy they should be made on the 'cured and nearly cured' patients and again on the cured patients four weeks after cure. Positive results will have larger def- that the fungicide has not possibility that fungi are any event this mycologic

data may be available when making final evaluation. The competence of the examiner in recognition of fungi is of paramount importance.

(1) Grading of Results: "Cured," "almost cured," "improved," "stationary" and "worse" are suggested, but each worker is at liberty to select any system that suits his purposes. For his own guidance he should be sure beforehand of the criteria for grading; from this there should be no deviation later. A subdivision like this into five grades reduces the number of cases available for subsequent statistical purposes and illustrates once again the necessity for numerous patients to begin with. Opinions of patients as to results should not be depended on too much; in cases of doubt they should be discounted. Patients commonly regard themselves as cured when itching ceases. It will be conducive to accuracy if the physician has an assistant who will independently grade the results, the final grading being decided in consultation on the spot.

3. Toxicity Tests.—These should be performed depending on the individual circumstances surrounding the chemical concerned. Where there is a hazard, the Bureau of Ships circular entitled "Disinfectant, Germicide and Fungicide," page 4, paragraph F.—2d may be followed. Ten healthy adult albino rats weighing between 150 and 250 Gm should be employed, none pregnant. They should be fed as usual. Three-tenths cc. of the fungicide (standard strength) per kilogram of body weight should be slowly inserted obliquely into the peritoneal cavity. The animal should then be given the usual food and water and observed for untoward effects for 72 hours.

ALCOHOLS

ISOPROPYL ALCOHOL.—Obtained by the reduction of acetone or, as a product in the petroleum industry, by the absorption of olefin gases containing propylene in sulfuric acid, and hydrolyzing the resulting sulfuric acid esters. The structural formula may be represented as follows:



For description and standards, see The National Formulary 1st supplement under Isopropyl Alcohol and National Formulary under Isopropyl Alcohol Rubbing Compound.

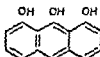
Recent investigations indicate that
as far as
it does not
close

of solutions or insulin it has been employed as a disinfecting agent in connection with the administration of this agent. Iso propyl alcohol has been used for the removal of creosote from the skin.

by mouth

ANTHRACENE DERIVATIVES

ANTHRALIN—1,8,9 Anthratriol Anthralin may be represented by the following structural formula



For tests and standards see Section B

Actions and Uses—Anthralin is recommended as a substitute for chrysarobin in the treatment of psoriasis having the advantage of less liability to production of dermatitis less tendency to produce conjunctivitis when used about the face and scalp and less tendency to discolor the skin. The preparation has also been recommended in the treatment of chronic dermatomycosis and for stimulating action in chronic dermatoses.

Dosage—Anthralin is generally employed in concentrations of from 0.1 per cent up to 1.0 per cent in ointments or creams. It is always well to begin with smaller dosages because of a tendency to irritate the skin.

ABBOTT LABORATORIES

Ointment Anthralin 0.1% 0.25% 0.5% and 1% Anthralin in petrolatum base

Anthralin Cream 0.1% 0.25% and 0.5% Anthralin in a vanishing cream base of potassium stearate potassium oleate and distilled water

ANTIBIOTICS

TYROTHRICIN—An extract first isolated by Dubos obtained from *Bacillus brevis* a gram positive aerobic spore forming soil organism. Tyrothricin possesses antibacterial action against several species of gram positive organisms.

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lar
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use

Included in the organisms that show some degree of susceptibility are species of pneumococci streptococci and staphylococci.

Its action on bacteria appears to consist, at least in part, of inhibiting enzymatic action, retarding growth and causing lysis of the bacteria against which it is effective. Its strength is determined at present by the protection afforded mice infected with pneumococci administered intraperitoneally.

Tyrothricin should be applied locally. It is ineffective when administered orally and is ineffective and dangerous when given intravenously. It has been reported to be of value in the treatment of superficial indolent ulcers, the predominating organism of which is gram positive, mastoiditis, empyema and some other wound infections. Its field of usefulness is limited and it appears to exert no effect unless it can come in direct contact with the organisms. Thus it may not exert much effect in the presence of deep-seated infections. Body fluids such as saliva, urine and serum offer a slight inhibiting action, whereas substances from gram-negative organisms are decidedly inhibiting.

It may be used with caution in body cavities as long as there is no direct connection with the blood stream. But in no instance should proper surgical treatment be ignored when it is indicated. It should be remembered that, although tyrothricin appears to have a field of usefulness in medicine, its use is still in an experimental stage and much work remains to be done before its true status is established and final comparisons can be made with other antibiotics and anti-infective agents in general. Routine or indiscriminate use of solutions of tyrothricin for irrigation of the paranasal sinuses or other infected cavities close to the subarachnoid space following surgery should be avoided because of the danger of chemical meningitis that has been reported to occur following such application of this agent.

Dosage.—Tyrothricin must be applied locally, not intravenously or by mouth. It is administered after diluting with sterile distilled water to form an isotonic solution in a concentration which yields 500 micrograms of the drug per cubic centimeter. This concentration is usually effective against the infecting organism, although higher concentrations may be used if indicated. However, higher concentrations may be irritating to the tissues.

PARKE, DAVIS & COMPANY

Solution Tyrothricin 2%: 10 cc. vials. Each cubic centimeter contains 20 mg. of tyrothricin in alcohol 92 per cent.

S. B. PENICK & COMPANY

Tyrothricin: Bulk, 100 Gm., 500 Gm. and 1,000 Gm. glass jars.

SHARP & DOHME, INC.

Solution Tyrothricin Concentrate: 10 cc. and 20 cc. vials of a solution of tyrothricin, 25 mg. per cc. in alcohol 25 per cent and propylene glycol 75 per cent

CRESOL AND DERIVATIVES

Cresols are phenols in which one of the ring hydrogen atoms has been replaced by CH_3 . This substitution increases the germicidal efficiency, while the toxicity is not increased at least not in the same ratio. The cresols, therefore, possess distinct advantages as disinfectants. In practice, they are much less toxic than phenol because they are used more diluted but they are far from being "nonpoisonous." Another advantage of the cresol preparations over phenol is their lower cost. Their disadvantages are the disagreeable odor which depends mainly on im-

of soap, as in
several other
determination

ee isomers of
aining two or

more methyl groups are generally referred to as cresylic acid. They have a higher phenol coefficient.

The toxicity and local actions of the cresols, as of other phenols, may be diminished by "masking" the active OH group by the formation of esters.

meta CRESYLACETATE — Cresatin-Sulzberger (SHARP & DOHME) — The structural formula of *meta* cresylacetate may be represented as follows:



For tests and standards, see Section B.

Actions and Uses. — *meta* Cresylacetate is said to possess ant-

suppuration due to ethmoid diseases, atrophic nasopharyngeal catarrhs, furunculosis of the external auditory canal and purulent otitis media. When applied to mucous membranes it is said to cause no irritation, sloughing or discomfort.

Dosage. — *meta* Cresylacetate may be employed either in the pure form or in dilution with oils or alcohol by direct application or spray.

SHARP & DOHME, INC.

Cresatin Metacresylacetate Sulzberger: 30 cc. glass stoppered bottles.

Ointment Cresatin Metacresylacetate Sulzberger: 7.1 Gm tubes. Contains metacresylacetate 80 per cent, with benzoic acid and ethyl-cellulose.

U. S. patent 1,031,971 (July 9, 1912; expired). U. S. trademark 80,533.

SURFACE ACTIVE ANTI-INFECTIVES

The local anti-infectives belonging to this group are substances which have the property of altering the physical properties of surface or interfaces. They are sometimes referred to as "detergents." They are usually subclassified as anionic, cationic or nonionic accordingly as they are negatively or positively charged or are unchanged on the chemical group of the compound that is responsible for the surface activity.

The members of the cationic group have far greater anti-infective action than have those of the other two groups. They are represented by fatty amine salts, the quaternary ammonium compounds, and the alkyl pyridinium compounds. The anion-active group is exemplified by ordinary soap, a true detergent, alkyl sulfates and salts of bile acids. The nonionic agents possess no significant germicidal activity and some may actually stimulate the growth of bacteria. The partial esters of polyhydric alcohols and fatty acids are representative of this class.

The mechanism whereby some surface active agents act as anti-infectives is not yet clearly understood. Attempts have been made to use these compounds to reduce the bactericidal action. That this bactericidal action of these compounds is apparent from the fact that many substances which are good surface tension depressors are poor anti-infectives at the concentrations at which the surface active compounds are used is not difficult to understand. Evidence of the anti-infective action of these compounds is possibly

The anti-infective action varies with the chemical constitution of these compounds and the pH to which they are adjusted. In general, the anionic agents are bactericidal only against gram-positive organisms; cationic agents are effective against both gram-positive and gram-negative organisms but higher concentrations are required to kill the latter type. Anionic agents work best in a more acid medium, whereas the anti-infective power of cationic agents increases as the pH is increased though in some instances the increase is not very great. The bactericidal action of surface active anti-infectives is reduced in the presence of serum, so that their phenol coefficient tested by methods not involving the addition of organic matter are subject to erroneous interpretation when applied to conditions of actual use.

Anionic

SODIUM TETRADECYL SULFATE—See section on Sclerosing Agents

Cationic

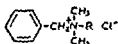
Cationic surface active anti-infectives bear positive electrical charges on their hydrophobic groups. Most of the commonly available anti-infectives belonging to this group are supplied at a pH slightly under 7.0. Since the bactericidal action of cationic compounds is opposed by that of anionic agents (soap in concentrations as low as 0.1 per cent is harmful), their application to the intact skin to be prepared for surgery has to be preceded by thorough rinsing of the soap-cleaned areas, first with water and then with 70 per cent alcohol. The use of alcohol diminishes the ionization of ordinary soap solution, so that the inactivating chemical union of soap with the disinfection is prevented.

The quaternary ammonium compounds form a film on skin under which organisms may remain viable.

Cationic detergents cannot be expected to provide positive disinfection of surgical instruments and rubber articles, since like most other types of disinfectants they possess little sporicidal activity. They may, however, be used for preservation of previously sterilized articles during storage. Manufacturers of Council accepted cationic disinfecting agents recommending such use are required to include on labels and in advertising a disclaimer of action against clostridial spores.

Some of the fatty amine salts appear to be primary irritants or skin sensitizers. Many of the quaternary ammonium compounds and the alkyl pyridinium compounds have been used as local anti-infectives for several years and very few instances of skin hypersensitivity have been reported.

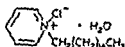
BENZALKONIUM CHLORIDE—U S P—Zephiran Chloride (WINTHROP-STEARNs).—Alkylbenzyltrimethylammonium chloride.—A mixture of alkylbenzyltrimethylammonium chlorides of the general formula $C_6H_5CH_2N(CH_3)_3RCl$, in which R represents a mixture of the alkyls from C_8H_{17} to $C_{18}H_{37}$. It contains, when calculated on a moisture free basis and the average molecular weight of 366, not less than 97 per cent and not more than 102 per cent of $C_6H_5CH_2N(CH_3)_3RCl$. U S P. The structural formula of benzalkonium chloride may be represented as follows:



For description and standards see the U S Pharmacopoeia under Benzalkonium Chloride and Benzalkonium Chloride Solution.

CETYL PYRIDINIUM CHLORIDE.—Ceepryn Chloride is the name of the quaternary salt of

The structural formula of cetyl pyridinium chloride may be represented as follows:



For tests and standards, see Section B.

Actions and Uses—Cetyl pyridinium chloride, a quaternary ammonium salt, is a cationic detergent that possesses useful surface-active as well as antiseptic properties. It is employed in aqueous solution or tincture in appropriate dilutions for topical application in the pre-operative disinfection of the intact skin and the prophylactic antiseptic of superficial minor wounds. It is also useful by topical application or irrigation for therapeutic disinfection of accessible mucous membranes and more extensive wounds or infections of the underlying tissues. It may also be used to preserve sterility of instruments during storage.

Cetyl pyridinium chloride is subject to the shortcomings of other cationic detergents employed as germicides in that its action is opposed by anionic detergents such as ordinary soap, may be reduced in the presence of serum and tissue fluids, and is not reliable against clostridial spores.

Dosage—For pre-operative preparation of the intact skin, a 1:100 aqueous solution may be used alone for scrubbing for a period of five to ten minutes; when the conventional soap-alcohol-ether-germicide method is to be employed, 1:500 or 1:1000 tincture dilutions may be used as the germicide if soap is thoroughly removed before application. Similar dilutions of the tincture or a 1:1000 aqueous solution may be used for topical application to minor lacerations and abrasions. For disinfection of delicate mucous membranes or extensive areas of exposed tissue, from 1:5000 to 1:10,000 solutions should be used.

THE Wm. S. MERRELL COMPANY

Isotonic Solution Ceepryn Chloride 1:1,000: 480 cc. and 3.84 liter bottles. Contains 0.1 per cent cetyl pyridinium chloride in distilled water made isotonic by addition of 0.26 Gm. of monobasic sodium phosphate and 1.43 Gm. of disodium phosphate per 100 cc.

Concentrated Solution Ceepryn Chloride 10%: 180 cc. An aqueous solution containing 10 Gm. of cetyl pyridinium chloride per 100 cc. of solution and

Tincture Ceepryn Chloride 1 200 (Tinted) 120 cc. 480 cc. and 384 liter bottles. Contains 0.5 per cent of cetyl pyridinium chloride in a tincture medium of 50 per cent ethyl alcohol by volume and 10 per cent acetone by volume.

Tincture Ceepryn Chloride 1 500 (Tinted or Untinted) 120 cc. 480 cc. and 384 liter bottles. Contains 0.2 per cent of cetyl pyridinium chloride in a tincture medium of 50 per cent ethyl alcohol by volume and 10 per cent acetone by volume.

U S patent 2 293 104 U S trademark 398 185

DYES

Dyes are used medically as antiseptics as chemotherapeutic agents and for special effects upon tissue cells. The local antiseptic action of dyes can be explained by their bacteriostatic and bactericidal powers. These are often relatively specific.

The dyes which have been introduced in medicine for the most part in the last decade are practically all organic synthetics. Roughly they may be divided into five classes: (1) the azo dyes of which scarlet red medicinal scarlet red sulfonate and dimazon are described in New and Nonofficial Remedies (these have been in use for considerable time); (2) the acridine dyes such as acriflavine hydrochloride (introduced as acriflavine), acriflavine base (introduced as neutral acriflavine[™]) and proflavine; (3) the fluorescein dyes either as fluorescein or combined with the metal mercury such as mercurochrome soluble and flumerin; (4) the phenolphthalein dyes such as phenolphthalein and phenolsulfonphthalein which are official in the U S Pharmacopeia and the chlorine bromine and iodine substitution products; (5) the triphenylmethane or rosaniline series which comprise a large list of substances used in the industries extensively in laboratory practice and more recently in medicine, such as gentian violet, crystal violet, methyl violet and fuchsin; (6) miscellaneous dyes such as methylene blue (methylthionine chloride U S P). Much confusion has existed concerning the composition of dyes; various manufacturers of commercial dyestuffs making similar dyes of varying composition both qualitatively and quantitatively. Usually the commercial dye contains a diluent such as dextrin or salts and is judged by tinctorial power. In order to obtain comparable results when employed clinically the dyes should be of constant composition preferably without diluent.

Azo Compounds

The azo dyes have been used in medicine for many years—more generally recalled under the name scarlet R (scarlet red). The exact constitution of the scarlet R dyes which have been used seems to have varied in minor details with different investigators. Chemically they have been azo compounds (that is they contain the linkage—N=N—) combined with betanaphthol. In New and Nonofficial Remedies a distinction between two scarlet red compounds has been made.

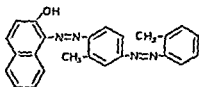
scarlet red medicinal Biebrich is described as tolylazotolyazobetanaphthol; scarlet red sulfonate is described as the sodium salt of azobenzenedisulfonic acid azobetanaphthol; it differs from the former in that the methyl group (CH_3) of the tolyl radicals has been replaced by sodium sulfonate ($-\text{SO}_3\text{Na}$) groups. The name "Biebrich scarlet red, medicinal" which occurs in medical literature, was erroneously applied in the first place; the name Biebrich scarlet is used in dye indexes only for the dye here listed as scarlet red sulfonate.

Actions and Uses.—Scarlet red medicinal Biebrich and scarlet red sulfonate have been claimed to have a marked power of

burns, wounds, chronic ulcers, etc. In chronic ulcers, however, it is requisite that the local circulation be good in order to obtain a permanent result.

Dosage.—The scarlet red preparations are generally used in the form of an ointment containing from 4 to 8 per cent of the substance. The 8 per cent ointment is somewhat irritating and should be alternated with a soothing ointment.

SCARLET RED-N. F.—Sudan IV.—Scarlet Red, Medicinal.—Biebrich Scarlet Red—"An azo dye, *o*-tolyl azo-*o*-tolyl azo- β -naphthol." N. F. The structural formula may be represented as follows:



For description and standards see The National Formulary under Scarlet Red and Scarlet Red Ointment.

Actions, Uses and Dosage.—See general article, Azo Compounds.

HEILKRAFT MEDICAL COMPANY

Scarlet Red Salve: Scarlet red medicinal, 8 parts, eucalyptol, 2 parts, and petrolatum, 90 parts

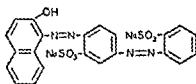
MERCK & Co., INC.

Scarlet Red Medicinal Biebrich (*Powder*): Bulk.

NATIONAL ANILINE DIVISION, ALLIED CHEMICAL & DYE CORPORATION

Scarlet Red Biebrich Medicinal (*Powder*): Bulk.

SCARLET RED SULFONATE—Biebrich Scarlet, water soluble—The sodium salt of azobenzenedisulfonic acid azobeta-naphthol—The structural formula may be represented as follows



For tests and standards, see Section B

Actions, Uses and Dosage—See general article, Azo Compounds

NATIONAL ANILINE DIVISION, ALLIED CHEMICAL & DYE CORPORATION

Scarlet Red Sulfonate (*Powder*): Bulk

PARKE, DAVIS & COMPANY

Ointment Scarlet Red 5%: Scarlet red sulfonate, 5 parts, petrolatum containing a small amount of wax, 95 parts

Ointment Scarlet Red 10%: Scarlet red sulfonate, 10 parts, petrolatum containing a small amount of wax, 90 parts

Acridine Derivatives

The acridine derivatives are mostly yellow dyes—acridine dyes obtained from coal tar—to which the term “flavine” has been applied (“flavine” should more correctly be applied to a vegetable coloring matter). The representative acridine dyes used in medicine are acriflavine hydrochloride (introduced as ‘trypaflavine’ and ‘acriflavine’), acriflavine base (introduced as “neutral trypaflavine” and “neutral acriflavine”), and proflavine. In 1912, Ehrlich found that the acridine dye diamino-methylacridinium chloride hydrochloride possessed therapeutic properties when used in trypanosome infections and hence he termed it *trypaflavine*. Later this substance was investigated in England, particularly in regard to its effects as a wound antiseptic, and the name “acriflavine” was applied to it. In a generic sense the terms “trypaflavine” and “acriflavine” have been applied both to acriflavine base and acriflavine hydrochloride. Another closely related substance diaminoacridine monohydrogen sulfate, was studied also, to which was given the name ‘proflavine’. A considerable number of bacteriologic and clinical reports on these substances have been published. It appears to be established that these dyes possess marked antiseptic and germicidal properties and on this account they have been employed in a number of pathologic conditions.

Actions and Uses.—The antiseptic or bacteriostatic action of acriflavine hydrochloride and proflavine appears to be weakened in the presence of serum. In the treatment of wounds, it is claimed that these drugs are comparatively free from toxic or irritant action on living tissues and that they do not inhibit appreciably the phagocytic action of the leukocytes. Acriflavine hydrochloride is claimed to exert a specific bactericidal action

it has a greater

action is slower.

flavine base and

of wounds, ure-

thritis, gingivitis, gonorrheal conjunctivitis, blenorrea, eczema, furunculosis,

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riflavine

hydrochloride has been suggested in areas where freedom from irritation (due to the acid reaction of acriflavine hydrochloride and proflavine) is desirable. The intravenous use of acriflavine base has been proposed, but critical evidence for its necessity is lacking.

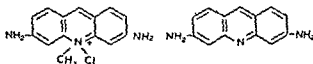
Dosage.—In the treatment of wounds, the solution generally employed is 1 in 1,000 in physiological solution of sodium chloride, although weaker solutions may be used. In suppurating wounds, this solution is used for syringing and swabbing the wound after free incision, for irrigation after providing adequate drainage, and for saturating the gauze with which the wound is finally covered. Evaporation should be prevented by protective dressing. In cavities, gauze saturated with the solution may be used as a light packing. Fresh wounds are cleansed thoroughly with the solution, and as much of the solution as possible is left in contact with the injured surfaces. Such wounds may be closed by suture and may be expected to heal by first intention.

In the treatment of open wounds, an ointment has been used which contains 1 per cent of proflavine oleate (prepared from proflavine base) in an ointment base composed of equal parts of petrolatum and calcium carbonate. A thick layer of the ointment may be spread on gauze and applied to the surface of the cleansed wound, or the ointment may be spread on the wound directly. The primary dressing need not be changed for several days.

In gonorrhea, a strength of 1 in 1,000 in isotonic solution of sodium chloride may be used for injection into the urethra. For irrigation, when relatively large quantities are to be used, a 1 in 4,000 solution is preferable because it is less irritating; solutions of from 1 in 6,000 to 1 in 10,000 have been used. In throat infections a spray of 1 in 1,000 solution is used. In middle ear suppurations a 1 in 500 solution in 50 per cent alcohol is dropped into the ear or the cavity may be packed with gauze wet with the solution. In gingivitis the mouth is irrigated with a 1 in 1,000 solution. Solutions of acriflavine

hydrochloride crystals may be used and crystals may be heated as

ACRIFLAVINE N F—Acriflavine Base—Neutral Acriflavine—A mixture of 2,8 diamino-10 methylacridinium chloride and 2,8 diaminoacridine containing when dried to constant weight at 100° C not less than 13.3 per cent and not more than 15.8 per cent of Cl N F The structural formulas of these compounds (which are now properly named 3,6 diamino-10 methylacridinium chloride and 3,6—diaminoacridine) may be represented as follows



For description and standards see The National Formulary under Acriflavine

Actions Uses and Dosage—See general article Acridine Derivatives

ABBOTT LABORATORIES

Acriflavine (Powder) Bulk

Enterab Acriflavine 30 mg and 100 mg Each tablet is enteric coated with a resin prepared from stearic acid, phthalic anhydride and glycerine

U. S. trademark 353 674

Tablets Acriflavine 0.1 Gm. One tablet dissolved in 100 cc. of isotonic solution of sodium chloride makes a 1:1000 solution

Tablets Acriflavine 30 mg One tablet dissolved in 30 cc of isotonic salt solution makes a 1:1000 solution.

NATIONAL ANILINE DIVISION ALLIED CHEMICAL & DYE CORPORATION

Acriflavine (Neutral) (Powder) Bulk.

Acriflavine "Pro Injection" (Neutral) 0.5 Gm. and 10 Gm. vials

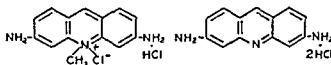
Ointment Acriflavine (Neutral) 1% Acriflavine 1 part, dissolved in glycerin 8 parts and incorporated with a base composed of hydrous wool fat and petrolatum to make 100 parts

Tablets Acriflavine (Neutral): 0.1 Gm.

Enteric Coated Tablets Acriflavine (Neutral): 32.4 mg. Each tablet is coated with phenyl salicylate containing some keratin.

Troches Acriflavine (Neutral): Each troche contains neutral acriflavine, 6 mg.; menthol, 0.6 mg. and sodium chloride, 0.6 mg.

ACRIFLAVINE HYDROCHLORIDE-N. F.—"A mixture of the hydrochlorides of 2,8-diamino-10-methylacridinium chloride and 2,8-diaminoacridine containing when dried to constant weight over sulfuric acid, not less than 23 per cent and not more than 24.5 per cent of these compounds
10-methylacridinium
represented respectively, as follows.



For description and standards see The National Formulary under Acriflavine Hydrochloride.

Actions, Uses and Dosage.—See general statement on Acridine Derivatives.

ABBOTT LABORATORIES

Acriflavine Hydrochloride (Powder): Bulk.

NATIONAL ANILINE DIVISION, ALLIED CHEMICAL & DYE CORPORATION

Acriflavine Hydrochloride (Powder): Bulk. Controlled biologically so that the maximum nonlethal dose for mice weighing 20 Gm. shall not exceed 15 mg.

To determine the maximum nonlethal dose the drug is dissolved in water in such concentration that 1 cc. contains the quantity to be administered. A series of mice weighing 20 Gm. each are injected subcutaneously with small doses of the drug, each succeeding animal receiving an increase of $\frac{1}{10}$ mg. of the drug over the preceding one. The dosage under which all of the animals survive and over which all die is the maximum nonlethal dose.

DYMIXAL (McNEIL).—A mixture of three dyes containing crystal violet 46 per cent, brilliant green 31 per cent and acriflavine 23 per cent. It may be prepared by mechanical mixing of the three dyes in their solid state.

For tests and standards, see Section B.

Actions and Uses.—This mixture is proposed for the treatment of burns. It possesses antiseptic action and forms a flexible

eschar. It appears to be more advantageous than a single dye in antiseptic effect against gram-positive and gram-negative bacteria.

Dosage—This dye mixture may be applied directly to the wound as a jelly or as a 2.6 per cent aqueous solution. If an oily substance has been used it should be removed before the dye mixture is applied. Blebs should be excised and loose pieces of skin removed. When the solution is applied, a new application can be made as fast as each one dries, the usual procedure requiring about six applications. The jelly may also be applied in several applications, being spread thinly during each application.

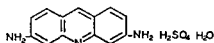
MCNEIL LABORATORIES

Dymixal (Powder). 6.5 Gm. and 65 Gm. bottles

Dymixal Jelly 2% 56.7 Gm. collapsible tubes. A water-soluble jelly containing 2 per cent of the dye mixture, glycerin 5 per cent, methyl cellulose 5 per cent and water.

U. S. trademark 378,611

PROFLAVINE SULFATE-N. F.—Proflavine—3,6-Diaminoacridinium monohydrogen sulfate monohydrate. The structural formula may be represented as follows:



For description and standards see The National Formulary under Proflavine Sulfate.

Actions, Uses and Dosage—See general article, Acridine Derivatives.

NATIONAL ANILINE DIVISION, ALLIED CHEMICAL & DYE CORPORATION

Proflavine (Powder) Bulk. Controlled biologically so that the maximum nonlethal dose for mice weighing 20 Gm. does not exceed 6 mg.

Triphenylmethane (Rosaniline) Derivatives

Of the derivatives of triphenylmethane and its homologue

the red color of pararosaniline chloride or fuchsine is changed

to violet as methyl groups are substituted for the hydrogens in the amino groups. The intensity of the violet color is augmented in direct proportion to the increase in the number of methyl groups. There are three closely related triphenylmethane derivatives, namely gentian violet, crystal violet and methyl violet. Gentian violet is hexamethylpararosaniline chloride with an admixture, usually of pentamethylpararosaniline and tetramethylpararosaniline chlorides; by some it is defined as a mixture of

tive also. Hence, one definition of gentian violet is practically the same as the other. It seems likely that in therapeutics it will

used. The material which has been used by the workers so far, however, has been gentian violet.

Gentian violet was introduced as an antiseptic by J. Stelling in 1890 and has been advocated by Churchman, who found that solutions of the dye had a selective action on certain bacteria and that the majority of gram-negative organisms survived exposure to

it. mar-
hile the
tive ac-
ly when

the organisms are exposed to the dye with slight elevation of temperature (about 50 C.). Acid fuchsin is incompatible with gentian violet, and the compatibility of all mixtures of dyes should be determined before any combination is prepared. Churchman claimed, however, that acriflavine possesses much the same selectivity as acid fuchsin, so he proposed the use of a mixture of these two dyes. The effectiveness of such a solution has not yet been established clinically. Aldrich [New England J. Med. 217: 911 (1917)] reported that a dye-mixture of gentian violet and neutral acriflavine 1 part by

in 100 cc. of water to make a solution for spraying burns that is reported to produce a suitable eschar and reduce infection. None of the rosaniline dyes is a strong bactericide.

It is employed for the treatment of super-

principal disadvantage is the staining of clothing that may occur with their use

CARBOL-FUCHSIN PAINT—Carfusin (ROBER)—A solution containing boric acid 1% phenol 4.5% resorcinol 10% fuchsin 0.3%, acetone 5% and alcohol 10% in water q s

The boric acid phenol resorcinol fuchsin and acetone used in the preparation of this particular preparation meet the requirements of the U S Pharmacopeia or The National Formulary

Actions and Uses—Carbol fuchsin paint is a stabilized preparation of the original basic fuchsin formula known as Castellani's paint that is widely employed for topical application to superficial fungus infections of the skin Its use should be restricted to subacute or chronic dermatophytoses it has been found to be of value for epidermophytosis interdigitalis pedum ("athlete's foot"), other intertriginous lesions of fungus origin, *Tinea trichophytina* (ringworm) and *Tinea imbricata*.

Carbol fuchsin paint has the advantage over the original and subsequently modified preparations in that it is stable but it should be protected against evaporation It shares with other triphenylmethane dyes the disadvantage that it will stain clothing with which it comes in contact It should never be applied to large areas of the body or to patients with particularly sensitive skins A test application of a 1:3 dilution should be made to a single small lesion before beginning treatment with the full strength paint It should be properly guarded against accidental ingestion because of the poisonous character of the ingredients

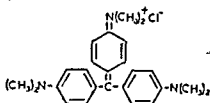
Dosage—Carbol fuchsin paint is applied full strength directly to the surface of the skin lesions Thorough topical application once or twice daily is indicated in subacute phases three times daily in chronic or particularly stubborn lesions Interim use of a foot powder and twice daily change of hosiery is recommended in the treatment of epidermophytosis pedis In cases associated with excessive drying of the skin application of the paint may be continued in conjunction with applications of either boric acid ointment containing 2 to 5 per cent of ammoniated mercury or an ointment of petrolatum containing 1 per cent each of sulfur and salicylic acid and 25 per cent each of zinc oxide and talc.

WILLIAM H ROBER INC

Carfusin: 30-cc. and 120 cc bottles A solution of boric acid 1% phenol 4.5% resorcinol 10%, fuchsin 0.3% acetone 5% and alcohol 10% in water q s

U S trademark applied for

METHYLOSANILINE CHLORIDE U S P.—Gentian Violet Methyl Violet Crystal Violet—Hexamethylparosaniline usually admixed with pentamethylparosaniline chloride and tetramethylparosaniline—U S P The structural formula of hexamethyl β rosaniline chloride may be represented as follows



For description and standards see the U. S. Pharmacopeia under Methylosaniline Chloride and The National Formulary under Methylosaniline Chloride Jelly and Methylosaniline Chloride Solution

Actions and Uses.—Methylosaniline chloride is a useful antiseptic for infected wounds, mucous membranes and serous surfaces.

Strongyloides infestation.

Dosage.—60 mg. U. S. P. For direct application, a solution of from 1 in 500 to 1 in 1,000 may be employed; for instillation, a 1 in 10,000 solution.

THE COLEMAN & BELL COMPANY, INC.

Gentian Violet Improved Medicinal (Powder): Bulk Gentian violet medicinal.

NATIONAL ANILINE DIVISION, ALLIED CHEMICAL & DYE CORPORATION

Gentian Violet Medicinal (Powder): Bulk.

Tablets Gentian Violet Medicinal: 32.4 mg.

Enteric Coated Tablets Gentian Violet Medicinal: 32.4 mg. The tablets are coated with phenyl salicylate containing some keratin.

FORMALDEHYDE

The antiseptic actions of formaldehyde cannot be utilized directly on the body because of the irritant and coagulant effects. Attempts have been made to avoid these effects by enclosing the formaldehyde in such a way as to cause it to dis-
 cure
 ill be
 eptic
 mine
 effects

are confined to acid fluids and therefore, essentially to the urine. Other compounds are effective mainly through the other constituents with which the formaldehyde is combined rather than through the formaldehyde itself

The wide reactivity of formaldehyde gives the possibility of a great variety of compounds with proteins, carbohydrates, amides, phenols and aromatic derivatives. Methenamine does not contain formaldehyde as such but liberates it under certain conditions (See systemic anti infectives)

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v
L



For description and standards see the U S Pharmacopeia under Formaldehyde Solution.

Actions, Uses and Dosage—Formaldehyde solution is germicidal in the strength of from 1 to 2 per cent (percentages refer to amounts of absolute formaldehyde HCHO) but the action may be delayed from 20 to 30 minutes. In the concentration of 1 in 5000 it restrains the growth of many organisms and in many cases a strength of 1 in 20 000 or 1 in 30 000 is sufficient to prevent the multiplication of bacteria. Formaldehyde solution

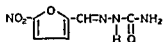
alcohol are
sometimes
the hands
The use of
formaldehyde for the preservation of food is condemned.

MERCK & Co INC.

Solution Formaldehyde Bulk

FURAN DERIVATIVES

NITROFURAZONE—Furacin (EATON LABS.)—5 nitro-2 furaldehyde semicarbazone. A synthetic antibacterial substance derived from furfural possessing the following structural formula



For tests and standards, see Section B.

Actions and Use.—Nitrofurazone is a yellow compound possessing antiseptic properties. It is inhibitory in the laboratory to a wide range of bacteria to 1:200,000 and bacilli to 1:500,000. It is not soluble in much less than 5,000 parts of water. It is effective in vitro and in vivo against a variety of gram-negative and gram-positive bacteria; it has least bacteriostatic activity against *Pseudomonas aeruginosa* and little bactericidal effect on *Diplococcus pneumoniae*.

Nitrofurazone is useful for topical application in the prophylaxis and treatment of superficial mixed infections common to contaminated wounds, burns, ulceration and certain diseases of the skin. It is sometimes of value for the treatment of ecthyma. It may be useful as an adjunct to surgery in the preparation of areas for skin grafting and in the treatment of osteomyelitis. Daily application for periods of one month or longer may produce a local reaction in a small percentage of cases. Sensitivity or intolerance to its local use has been observed and may be

showing induced resistance to sulfathiazole, penicillin or streptomycin are as susceptible to nitrofurazone as their parent strains. Induced resistance to the aforementioned agents does not entail resistance to nitrofurazone.

Systemic toxicity due to absorption of the compound is considered unlikely. Clinical studies indicate that the ingestion of 1 to 2 Gm. daily for long periods is fairly well tolerated by the

Dosage.—Nitrofurazone is used topically in an ointment-like base containing a concentration of 1:500 (0.2 per cent). It is applied locally either directly or to dressings that cover the infected area. The base is water soluble but softens at body temperature and may thus require special coverings to maintain effective contact with certain areas to which it may be applied. Dressings may be reinforced with cellophane or similar material, and petrolatum gauze may be used for a barrier to limit the absorption into the dressing. On exposure to light, the bright yellow nitrofurazone turns dark brown. This is not associated with any ill effects and may be avoided by covering with light dressings.

EATON LABORATORIES, INC.

Furacin Soluble Dressing 1·500· 113 Gm., 454 Gm and 226 Kg jars Each hundred grams contains nitrofurazone 0·2 Gm, Carbowax (1540) 30 Gm, Carbowax (4,000) 15 Gm and polyethylene glycol (300) 54·8 Gm

Solution Furacin 1·500 118 cc. and 473 cc bottles Each 100 cc contains nitrofurazone 0·2 Gm and polyethylene glycol of monoiso-octyl phenyl ether 0·3 Gm in a mixture of polyethylene glycol (300), 32·5 Gm, Carbowax (1,540), 32·5 Gm, and water

U S patent 2 319 481 (expires 1962) 2 416 234 (expires 1964), U S trademark 403 279

HALOGEN COMPOUNDS

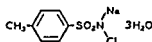
Chlorine Derivatives

The germicidal act is well known. In the employment of chlorine solutions of sodium potassium hypochlorite (Javelle water)

Hypochlorite preparations are fairly stable in the presence of alkali, and alkaline hypochlorite preparations have the added advantage that the alkali has a destructive and solvent action on most bacteria and other organic matter. In the treatment of infected wounds with hypochlorite solutions, an excessive degree of alkalinity is held to be objectionable on the grounds that it causes destruction of normal tissue and irritation of the skin.

On the theory that the action of hypochlorites is dependent on the combination of their active chlorine (Cl^+) with the nitrogen of protein certain organic preparations containing a chloramide group, which are practically neutral and relatively stable, have been proposed as substitutes

(Chloramine-T) — Chloramine-T structural formula



For description and standards see The National Formulary under Chloramine T

Actions and Uses—The actions of chloramine-T are essentially similar to those of diluted sodium hypochlorite solution.—N F It has the advantages of greater stability convenience of preparation, and the production of less irritation.

On the other hand, it lacks the solvent action of alkaline hypochlorites.

It is practically nontoxic, but should not be used by mouth, since it is decomposed by the gastric juice.

Dosage.—Chloramine-T is used in 0.1 to 4 per cent aqueous solution. For wounds, the normal strength is from 1 to 2 per cent, applied by the same technic as the surgical solution of chlorinated soda. It has also been employed for irrigation of the urethra, bladder and uterus, and as a mouth wash.

ABBOTT LABORATORIES

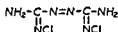
Chlorazene (Powder): 37.8 Gm., 189 Gm., 454 Gm., and 2.27 Kg. bottles.

Aromatic Chlorazene (Powder): 56 Gm., 113 Gm., 454 Gm., and 2.27 Kg. bottles. Chloramine-T, 5 per cent; sodium bicarbonate, 5 per cent; eucalyptol, 2 per cent; saccharin, 1 per cent; sodium chloride, 87 per cent.

Tablets Chlorazene: 0.3 Gm.

U. S. trademark 119,014.

CHLOROAZODIN-U. S. P.—Azochloramid (WALLACE & TIERNAN).— α, α' -azo-bis(chloroformamidine).—"Contains the equivalent of not less than 37.5 per cent and not more than 39.5 per cent of active chlorine (Cl)."—U. S. P. The structural formula may be represented as follows:



For description and standards see the U. S. Pharmacopeia under Chloroazodin and Solution of Chloroazodin.

Actions and Uses—Similar to those of a dilute solution of

suitable for lavage of wounds, and for irrigations or instillations into cavities. It is claimed that short exposure of epithelial tissue to aqueous solutions is harmless and that solutions of chloroazodin in vegetable oil (1:2,000) are applicable to the mucous membrane of the vagina, colon, and rectum. The available evidence indicates that chloroazodin possesses relatively low toxicity and is a relatively nonselective bactericidal agent.

Dosage.—Chloroazodin is usually employed in wounds in a dilution of 1:3,300 in an approximately isotonic solution buffered at pH 7.4. Greater dilutions up to 1:13,200 are proposed for use on mucous membranes. On June 1, 1937, a stable solution was prepared.

WALLACE & TIERNAN PRODUCTS, INC.

Saline Mixture of Azochloramid (Powder): This contains chloroazodin 3.17 per cent, sodium chloride 89.56 per cent, monopotassium phosphate 0.95 per cent, and sodium phosphate exsicc. 6.32 per cent by weight. Bottles of the powder containing 35.93 Gm. for preparing 1 gallon of aqueous solution of Azochloramid (1:3,300).

Surface Active Saline Mixture of Azochloramid (Powder): This contains Azochloramid 4.7 per cent, Sodium Chloride 89.56 per cent, Monopotassium Phosphate 0.95 per cent, and Sodium Phosphate exsicc. 6.32 per cent by weight. Bottles of the powder containing 35.93 Gm. for preparing 1 gallon of aqueous solution of Azochloramid (1:3,300). Bottles of the powder containing 35.93 Gm. for preparing 1 gallon of aqueous solution of Azochloramid (1:3,300).

Solution Azochloramid in Triacetin (1:500). 54 cc., 400 cc., 1,000 cc. and 4,000 cc. containers. A solution containing chloroazodin 1 Gm. in 500 Gm. of triacetin. Triacetin is a mixture of glyceryl acetates containing approximately 95 per cent of glyceryl triacetate.

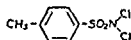
Strong Solution of Azochloramid in Triacetin (1:125). 50 cc. bottles. A solution containing chloroazodin 1 Gm. in 125 Gm. of triacetin for use in the preparation of Azochloramid in vegetable oil (1:2,000).

U. S. patent 2,073,256 (March 8, 1937, expires 1954)

Tablets Saline Mixture of Azochloramid. Each tablet contains 0.55 Gm. of the Saline Mixture of Azochloramid for preparing 60 cc. of the aqueous solution of Azochloramid (1:3,300).

U. S. patent 1,958,370 (March 8, 1934, expires 1951) U. S. trademark 322,242

DICHLORAMINE-T — N.F. — *p*-Toluenesulfondichloramide — Dichloramine — "Dichloramine-T" contains the equivalent of not less than 28 per cent and not more than 30 per cent of active Cl² N. F.



For description and standards see The National Formulary under Dichloramine-T.

It is a powerful germicide, acting gradually, sustained antiseptic action.

It is more irritant than chloramine, but also more solvent. It should not be administered internally.

Dichloramine-T is claimed to be useful in the prevention and treatment of diseases of the nose and throat; it has been used with success when applied to wounds.

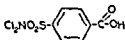
Dosage.—Dichloramine-T dissolved in chlorinated paraffin (which see) is used in concentrations of from 0.5 to 10 per cent. In nasopharyngeal work from a 1 to a 2 per cent solution is employed; for application to wounds a 5 per cent solution. The solution of dichloramine-T in chlorinated paraffin is not very stable and should not be kept for more than two or three days. At times the solutions may become irritating to the skin because of the formation of hydrochloric acid. Both dichloramine-T powder and solution should be protected from sunlight to prevent decomposition.

ABBOTT LABORATORIES

Dichloramine-T (Powder): Bulk.

It is a powerful germicide. It contains the equivalent of not less than 26.26 per cent of active chlorine.

Cl.—IV. P. The structural formula may be represented as follows:



For description and standard, see The National Formulary under Halazone.

Actions and Uses.—Halazone is said to be a powerful disinfectant.

thirty to sixty minutes, halazone in the proportion of from 1 in 200,000 to 1 in 500,000 sterilized polluted water contaminated with such organisms as *Bacterium coli*, *Bacterium typhosum*, *Bacterium paratyphosum* A and B, *Vibrio cholerae* and *Bacterium dysenteriae*.

Dosage.—For the sterilization of water, 4 to 8 mg. of hala-

zone, in the form of tablets containing sodium carbonate (or sodium borate) and sodium chloride, is added to 1 liter

ABBOTT LABORATORIES

Halazone (Powder): Bulk

Tablets Halazone: Halazone, 4 mg, sodium borate, 11 mg and sodium chloride sufficient to make about 0.13 Gm

SODIUM HYPOCHLORITE SOLUTION—Hyclorite (PENNSYLVANIA SALT Co.)—A solution of chlorinated soda, each 100 Gm. of which is stated to contain sodium hypochlorite 4.05 Gm, sodium chloride 2.50 Gm, calcium hydroxide 0.14 Gm, available chlorine

X, and is isotonic.

PENNSYLVANIA SALT MANUFACTURING CO

(Bethlehem Laboratories, Inc., Distributor)

Solution Hyclorite: Bulk

U. S. trademark 120 110

...lorosuccinimide —
...inchlorimide con
...per cent of active
...the structural formula may be represented as follows:



For description and standards see The National Formulary under Succinchlorimide and Succinchlorimide Tablets.

Actions and Uses.—Succinchlorimide is proposed for use in disinfection of water. Experiments indicate that succinchlorimide will disinfect water containing *Escherichia coli*, *Eberthella typhi*, *Salmonella paratyphi* A and B, *Vibrio cholerae* and *Shigella dysenteriae* within 20 minutes in dilution of 11.6 parts per million (approximately 1:100,000).

Dosage.—For the disinfection of water, 11.6 mg. of succinchlorimide per liter.

NATIONAL ANILINE DIVISION, ALLIED CHEMICAL & DYE CORP.
Succinchlorimide (Powder): Bulk.

Iodine and Iodine Derivatives

Certain iodine compounds are used for their local irritant and antiseptic effects, which are due probably to the action of free iodine contained in the preparations or liberated from them; or they may be administered for their systemic actions and for roentgen-ray diagnosis.

Iodine Preparations Containing Free Iodine

IOCAMFEN (SCHERING & GLATZ, DIV. OF WM. R. WARNER).—A liquid obtained by the interaction of iodine 10 parts, phenol 20 parts and camphor 70 parts, containing about 7.25 per cent free iodine.

For tests and standards, see Section B.

Actions and Uses—This preparation has the antiseptic and germicidal properties of iodine and the analgesic and stimulating properties of camphor and phenol.

It is used especially in the treatment and dressing of wounds, and in dentistry, also in ringworm of the feet, nails, and other parts of the body.

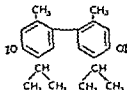
Dosage.—The preparation is applied in small quantities directly to wounds, the skin, cavities, etc., or on tampons or drainage material.

SCHERING & GLATZ, DIVISION OF WM. R. WARNER & CO., INC.
Iocamfen (Liquid): 30 Gm and 113 Gm. bottles.
U. S. trademark 112,934.

Iodine Dusting Powders

Preparations containing iodine in various combinations are used on granulating surfaces, abscesses, etc. The effects are ascribed to a slight stimulation of phagocytosis, and wound which renders it a less serious.

Iodoform has been the standard drug of this class. Other insoluble organic iodine compounds have been introduced to replace iodoform but with limited success. While they avoid the disagreeable odor and the occasional toxic systemic effects, they also lack much of the efficiency.



For description and standards see *The National Formulary* under Thymol Iodide.

Actions and Uses—Antiseptic, used chiefly as a dusting powder.

MERCK & Co. INC.

Thymol Iodide (*Powder*) Bulk.

WINTHROP STEARNS, INC.

Aristol (*Powder*) 30 Gm. bottles

U. S. trademark 17,393

ISOPARAFFINIC ACIDS

For tests and standards see Section B.

Actions and Uses—Coparaffinate ointment is for external use only. It should not be covered with thick tight bandaging, since irritation may result from this type of dressing. It is said to be of value in the treatment of pruritus ani and vaginae, mycotic infections of the hand and feet and eczemas of the ear and cer-

of iodine into the benzene ring of the phenol. The power of the phenol is increased by the addition of potassium permanganate with ph- in the b

Soluble compounds of bismuth used for their protective action should be employed with caution because of the danger of absorption of poisonous amounts of bismuth. Absorption of insoluble bismuth compounds from wounds and cavities occasionally occurs. Skin lesions similar to those sometimes following the use of arsphenamine are among the most important complications of bismuth therapy. For example, a pruritus, an erythema, an urticaria or a dermatitis, and rarely hemorrhagic lesions, are noted following bismuth therapy, and cases of agranulocytosis with angina have been reported. The administration of the drug should be stopped on the first sign of cutaneous irritation. Bismuth poisoning is indicated by a blue line on the gums, and by stomatitis. In some patients undergoing bismuth therapy systemic symptoms of malaise, nausea, headaches and vague rheumatic muscular and bone pains have been noted. Removal of the bismuth therapy is the principal treatment. Too free local application of bismuth containing powders or too free injection into cavities should be avoided. Large doses of bismuth subnitrate have produced nitrite poisoning by its reduction in the colon.

BISMUTH SUBNITRATE—N. F.—Basic Bismuth Nitrate—"A basic salt which, when dried over sulfuric acid for 18 hours, yields upon ignition not less than 79 per cent Bi_2O_3 [bismuth oxide]"—N. F.

For description and standards see The National Formulary under Bismuth Subnitrate and Bismuth Subnitrate Tablets

PARKE, DAVIS & COMPANY

Bismuth Paste Surgical: Bismuth subnitrate, one part, in yellow petrolatum, two parts

BISMUTH TRIBROMOPHENATE — Xeroform (SCHERING & GLATZ, DIV. OF W. R. WARNER) — A basic bismuth tribromophenate of variable composition

For tests and standards see Section D

Actions and Uses—Bismuth tribromophenate is claimed to be a nonirritating and nontoxic antiseptic. Occasionally cases of sensitization to its local use are noted. It is said to be valuable in ulcers cruris, in impetigo contagiosa, and in weeping eczemas, internally, in gastro-intestinal catarrh proctitis, dysentery, bacillary and choleraic diarrhea, cholera infantum.

Dosage—From 1 to 3 Gm. per day to adults, from 0.125 to 0.3 Gm. as a dose to children. Externally (as a dusting powder, in bandages, etc.) like iodoform, in lotions, and in ointments in 3 to 10 per cent strength.

SCHERING & GLATZ, DIVISION OF Wm. R. WARNER & Co., INC.

Xeroform (*Powder*): 30 Gm. and 453 Gm. bottles.

U. S. trademark 66,547.

Mercury

Compounds of mercury are used for the preparation of antiseptic and disinfecting solutions. They have a limited germicidal action and cannot be relied upon to kill bacterial spores even after several hours' exposure. Solutions of compounds of mercury with dyes or other organic radicals are used for antiseptics of the skin and are of distinct value in their bacteriostatic action. In general, these organic compounds of mercury are less toxic and less irritating than the older chlorides, iodides and cyanides of mercury. Claims for their ability to penetrate deeply into living tissue and to act as efficient chemotherapeutic agents after injection into the blood stream have not been established. Their antibacterial activity is greatly diminished in the presence of serum and other proteins.

INORGANIC

MERCURIC CYANIDE-N. F.— $\text{Hg}(\text{CN})_2$.—"When dried to constant weight over sulfuric acid, contains not less than 99 per cent of $\text{Hg}(\text{CN})_2$."—N. F.

For description and standards see The National Formulary under Mercuric Cyanide.

Actions and Uses.—Mercuric cyanide has been reported to be as actively antiseptic as mercuric chloride and to be less irritating; but this has been questioned. It is used locally and internally as is mercuric chloride. Blum and Schwab (*Presse Méd* 30:1081 [Dec. 16] 1922) highly recommended this drug as a diuretic in cardiac (but not in renal) disease. They give it in doses of 40 to 50 mg. by intravenous or intramuscular injection. They state, however, that mercury should be used as a diuretic only as a last resort when other drugs have failed.

Dosage.—Internally, from 4 to 8 mg., locally, solutions of from 1 in 4,000 to 1 in 2,000 may be used for applications to the eye or mucous membranes; from 1.5 to 2 cc. of a 1 per cent solution may be used hypodermically without causing local irritation. Death has occurred from the use of a vaginal injection containing 0.9 Gm. of mercuric cyanide.

In diphtheria and croup, it is used in 0.01 per cent solution as a gargle. In fibrinous rhinitis it is used on a tampon in 0.04 per cent solution.

MALLINCKRODT CHEMICAL WORKS

Mercuric Cyanide (*Powder*): Bulk.

MERCK & Co., INC.

Mercuric Cyanide (*Powder*): Bulk.

MERCURIC POTASSIUM IODIDE—A complex salt formed by the interaction of one molecule of mercuric iodide with two molecules of potassium iodide and containing about 25.5 per cent of mercury.

For tests and standards see Section B.

Actions and Uses—Mercuric potassium iodide is used for the same purposes as mercuric iodide over which it has some advantages because of its solubility. It is germicidal for many nonsporulating bacteria. However, there seems to be no work to show how much the activity is decreased when an excess of potassium iodide is present. In comparison with mercuric chloride it is claimed to have a greater safety factor. Weight for weight mercuric potassium iodide is about one half as toxic as mercuric chloride according to animal experiments in proportion to the mercury content, however mercuric potassium iodide and mercuric chloride possess about the same toxicity.

Externally mercuric potassium iodide is used for skin disinfection, irrigations and disinfection of instruments and of excreta and discharges.

Dosage—As a disinfectant it is used in concentrations of 1 in 100 to 1 in 10,000. For irrigation of wounds it is desirable to render the solution isotonic by addition of 0.9 per cent sodium chloride. Solutions of mercuric potassium iodide may be prepared

(1) By dissolving 1 part by weight of mercuric iodide and

(2) By dissolving mercuric potassium iodide in water containing potassium iodide. Solutions made from mercuric po-

PARKE, DAVIS & COMPANY

Discs Potassio Mercuric Iodide Each disc represents mercuric iodide 97.2 mg, potassium iodide 97.2 mg and sodium bicarbonate 2.9 Gm. Colored blue.

Discs Potassio Mercuric Iodide Each disc represents mercuric iodide 24.3 mg, potassium iodide 24.3 mg and sodium bicarbonate 1.04 Gm. Colored blue.

YELLOW MERCURIC OXIDE U. S. P.—Yellow Precipitate—When dried to constant weight at 110°C., contains not less than 99.5 per cent of HgO . —U. S. P.

For description and standards see the U. S. Pharmacopeia

under Yellow Mercuric Oxide and Yellow Mercuric Oxide Ointment.

Actions, Uses and Dosage.—principally as the official concentration of the salt is. It is used mainly for superficial infections. Because of its prolonged action frequent applications are unnecessary and undesirable.

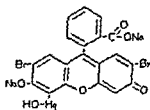
MANHATTAN EYE SALVE COMPANY, INC.

Ointment Yellow Oxide of Mercury 1%, Adrenalin Chloride 2%, and Phenol.—Yellow oxide of mercury, 1 per cent; solution of adrenalin chloride, 2 per cent; menthol, 0.04 per cent; phenol, 0.2 per cent; anhydrous wool fat, 10 per cent, and white petrolatum sufficient to make 100 per cent. Put up in collapsible tubes, for application to the eye.

ORGANIC

MERBROMIN-N.F.

"The disodium salt of . . . When dried to constant weight yields not less than 45 per cent and not more than 49.5 per cent of Hg [mercury], and not less than 18 per cent and not more than 21.3 per cent of Br. [bromine]."—N. F. The structural formula may be represented as follows:



For description and standards see The National Formulary under Merbromin, Merbromin Solution and Merbromin Solution, Surgical

Actions and Uses.—Merbromin is a nonirritating moderately active antiseptic. When applied to the skin, mucous membranes and wounds it exerts bacteriostatic action. The 2 per cent aqueous solution of merbromin acts more slowly than iodine

The drug is tolerated in a strength of 1 per cent by the bladder, renal pelvis and urethra; a 2 per cent solution applied to the anterior urethra causes only temporary discomfort. When tested by intravenous injection into rabbits, the danger point is

reached with a dosage of 25 mg per kg., and 5 mg causes a decrease in phenolsulfonphthalein excretion and an albuminuria which lasts about a week. Dogs are more resistant. No systemic effects have been observed following its local application in the human. Merbromin has been used in cystitis and urethritis also in affections of the eye and affections of the ear such as otitis media. Although merbromin has been used intravenously the Council does not recognize the use of the drug for this purpose. The intravenous injection may be followed by severe toxic symptoms.

Dosage—In the treatment of infections of the kidney pelvis the ureters are catheterized and the pelvis gently filled with a 1 per cent solution the catheter is plugged and the solution retained for five minutes. In the treatment of bladder conditions 25 to 30 cc. of the 1 per cent solution is introduced into the bladder and retained for one hour or longer the treatment being given daily or on alternate days or at longer intervals according to circumstances. Gonococcal infections are treated by more modern drugs. However when substances such as merbromin are indicated as adjunct treatment, they should be properly used. In anterior gonococcus urethritis, the anterior urethra is filled with a 1 per cent solution and the solution retained for five minutes. If the posterior urethra be involved, the solution is gently retained for an hour or more. In rare cases considerable irritation is produced particularly in those with residual urine. Later in the treatment of acute anterior gonorrhea a 2 per cent solution is used every three hours. Solutions should not be boiled. They should be made up from the drug itself as the tablets are not suitable for this purpose.

Merbromin is incompatible with acids with the salts of most alkaloids and with most local anesthetics. The aqueous solution stains the skin red but the discoloration may be removed by washing in a solution of sodium hypochloride.

HYNSON, WESTCOTT & DUNNING INC.

Mercurochrome (Powder) Bulk.

Solution Mercurochrome 2%

Surgical Solution of Mercurochrome Merbromin, 2 per cent dissolved in a vehicle consisting of 55 parts of 95 per cent alcohol 10 parts of acetone, and 35 parts of water to which has been added sodium carbonate 0.1 per cent.

Tablets Mercurochrome 0.3 Gm

U. S. patent 1,535,003 (Apr 21 1925 expired) U. S. trademark 19 149

PREMO PHARMACEUTICAL LABORATORIES INC.

Merbromin (Crystals) 10 Gm. 100 Gm., 500 Gm. and 1 000 Gm. bottles

Solution Merbromin 7.5 cc., 15 cc., 30 cc., 47.3 cc. and 178.5 cc. bottles

and 2.26 Kg. (5 lbs.) jars. Sodium ethylmercurithiosalicylate 0.1 per cent in a hydrophilic ointment base.

Ophthalmic Ointment Merthiolate 1:5,000: Contains sodium ethylmercurithiosalicylate 1 part in 5,000 parts of a base consisting of wool fat, liquid petrolatum and white petrolatum.

Solution Merthiolate, 1:1,000: One gram of sodium ethylmercurithiosalicylate and 1 Gm. of monoethanolamine in 1,000 cc. of water, buffered with 1.4 Gm. of sodium borate and containing sodium chloride to make the solution approximately isotonic.

Suppositories Merthiolate, 1:1,000: Each suppository weighs approximately 10 Gm. and contains sodium ethylmercurithiosalicylate 1:1,000 in a glycerin and gelatin base consisting of 17.3 parts glycerin and 7.6 parts gelatin.

Tincture Merthiolate, 1:1,000: Contains sodium ethylmercurithiosalicylate, 0.1 Gm., and monoethanolamine, 0.1 Gm., dissolved in alcohol, 50 cc.; acetone, 10 cc., and water, sufficient to make 100 cc.

U. S. Patent 1,672,615 (June 5, 1928; expired); 1,862,896 (June 14, 1932, expires 1949). U. S. trademark 252,182.

NITROMERSOL-N. F.—Metaphen (ABBOTT).—Anhydride of 4-nitro-3-hydroxymercuri-ortho-cresol. — $C_7H_5O_3NHg$. — "When dried to constant weight at 105 C., Nitromersol yields not less than 56 per cent and not more than 57.4 per cent of Hg."—N. F. When nitromersol is dissolved in alkali, the anhydride ring opens, forming the hydroxymercury salt. The structural formula of nitromersol may be represented as follows:



For description and standards see The National Formulary under Nitromersol, Nitromersol Solution and Nitromersol Tincture.

Actions and Uses.—Nitromersol is used only in the form of the sodium salt, which is claimed to be more germicidal than mercuric chloride when tested on cultures of *Staphylococcus aureus* and *Escherichia coli*. It is stated to be relatively non-toxic to mucous membranes or the skin and metallic instruments or rubber. Nitromersol is claimed to be relatively nontoxic.

Nitromersol is proposed for use in the treatment of gonorrhea and other infections of the eye; for the disinfection of skin, surgical instruments and rubber if no sporulating pathogenic organisms are present.

Dosage—Solutions of nitromersol in water are prepared with the aid of sodium hydroxide. For disinfection of instruments solutions of 1 in 5,000 to 1 in 1,000, for application to the skin solutions of 1 in 5,000 and 1 in 1,000, for ophthalmologic and for urethral irrigation solutions of 1 in 5,000 to 1 in 10,000 are proposed.

ABBOTT LABORATORIES

Ophthalmic Ointment Metaphen: Nitromersol 1/3,000 in an ointment base containing anhydrous wool fat, 25 per cent, and petrolatum, 75 per cent.

Solution Metaphen, 1:500: Nitromersol dissolved in water by means of sodium hydroxide to form the sodium salt of nitromersol.

Solution Metaphen, 1:2,500: Nitromersol dissolved in water containing 0.33 per cent each of sodium bicarbonate and sodium carbonate to form the sodium salt of nitromersol.

Disinfecting Solution Metaphen for Dental and Surgical Instruments: 946 cc and 3,785 cc bottles. Contains nitromersol 1:2,500 W/V and benzyl alcohol 40 per cent in an aqueous solution containing ethylene glycol 20.0 per cent W/V and sufficient sodium hydroxide and sodium carbonate to neutralize the metaphen.

Tincture Metaphen, 1:200: Nitromersol, 0.5 Gm., dissolved in a mixture of acetone, 10 cc., water, 40 cc. and alcohol, 50 cc.

U. S. patent reissue 17,563 (Sept. 22, 1925 expired) U. S. trademark 275,507.

Phenylmercuric Compounds

Phenylmercuric chloride and basic phenylmercuric nitrate were the first of the organic mercurial compounds of their type found to possess effective bacteriostatic and bactericidal activity against certain pathogenic micro-organisms. Evidence to indicate that other phenylmercuric salts are similarly effective suggests that the activity of such compounds is primarily attributable to the phenylmercuric ion, the structural formula of which may be represented as follows:



In general phenylmercuric compounds are used in the form of solutions or ointments. The following are the most commonly used:

HAMILTON LABORATORIES, INC.

Ointment Merphenyl Nitrate (Basic) 1:1,500: A water-in-oil emulsion ($\frac{2}{3}$ aqueous, $\frac{1}{3}$ oil phase) of an oxycholesterin base containing basic phenylmercuric nitrate 0.067 per cent with boric acid 0.1 per cent

Solution Merphenyl Nitrate (Basic) 1:1500: An aqueous solution of basic phenylmercuric nitrate 0.067 per cent with boric acid 0.1 per cent.

U. S. trademark 318,039.

For tests and standards, see Section B.

Phenylmercuric picrate in an acetone-

membranes should be kept in mind.

Dosage.—For prophylactic preoperative skin preparation, disinfection of soft tissue injuries and the treatment of superficial infections, tincture of phenylmercuric picrate 1:200 with picric acid 1.2 per cent is applied full strength; in wet dressings or

continuous irrigation for infected wounds a concentration of phenylmercuric picrate not greater than 1:15,000 should be used (prepared by diluting the 1:200 tincture approximately seventy five times with water). When used as a wet dressing undue concentration of the diluted solution from unavoidable evaporation should be prevented by the addition of about 0.5 per cent of sodium chloride. Approximately $\frac{1}{2}$ teaspoon of noniodized table salt to each pint of diluted tincture is recommended. This amount of sodium chloride does not produce excessive precipitation. The full strength (1:200) tincture should never be used to wet dressings or bandages.

HAMILTON LABORATORIES INC.

Tincture Merphenyl Picrate 1:200 with Picric Acid Bulk

U S trademark 318 039

Silver

Silver compounds are used in medicine to secure caustic astringent and antiseptic effects. These results are produced by the free silver ions. When caustic effects are desired silver nitrate is preferred because the colloidal compounds of silver are largely or completely lacking in caustic properties. As an astringent also silver nitrate is the compound of choice but it must be used in weaker solutions. Silver picrate acts similarly. The antiseptic action of silver nitrate is complicated by irritation, pain, astringency and corrosion. These may be desirable for the destruction of tissue or the stimulation of indolent wounds but when they are not necessary for such purposes they may be avoided by the use of colloidal silver preparations.

Caution. The long continued use of any silver preparation may produce irremediable discoloration of the skin or mucous membrane (argyria).

COLLOIDAL SILVER PREPARATIONS

In these the silver does not exist to any great extent as free ions, therefore it does not precipitate chlorides or proteins and is noncorrosive and relatively or quite nonastringent and nonirritant but a considerable degree of antisepsis is produced.

This is not proportional for the different compounds is due to the liberation of which vary for the different

The mechanism of the action of colloidal silver is analogous to that of the free silver ions.

in two stages: (1) the formation of a protective film on the surface of the bacteria which prevents the free silver ions from reaching the bacteria.

(2) the formation of a protective film on the surface of the bacteria which prevents the free silver ions from reaching the bacteria. The solution of the protein silver compounds that were formed in the first stage. If the second stage alone is desired (i.e. mild anti-

septics without irritation), the direct application of the colloid compounds may have advantages over their indirect production from silver nitrate, aside from the avoidance of irritation; for the absence of any coagulation membrane facilitates their access to the cells; they form more concentrated solutions than are likely to be formed from the re-solution of the silver precipitates *in situ*; the colloidal aggregates may be smaller and therefore more reactive; and because of the absence of irritation, they are likely to be more frequently applied and would for that reason secure a more continuous action.

The colloidal silver preparations appear to be quite efficacious for the prophylaxis against gonorrheal infection, evidently killing the organisms on direct contact. Culver (*J. Lab. & Clin. Med.*, 3:487 [May] 1918) reports that gonococci in hydrocele broth cultures are killed by momentary exposure to 0.5 per cent mild protein silver or to 0.25 per cent strong protein silver. As regards other organisms, discordant results have been reported.

Metallic silver and insoluble compounds of silver, such as the oxide, the halogen salts (iodide, chloride, etc.) and protein-silver precipitates, may be brought into "colloidal solution"; i.e., if they are sufficiently finely divided, they become miscible with water, so that they apparently go into solution (such "colloidal solutions" are strictly permanent "suspensions" of the insoluble substance in a state of ultramicroscopic particles). The commercial preparations are for the most part produced by dissolving reduced silver or silver oxide, or some protein-silver precipitate, in an excess of a denatured protein, and drying *in vacuo*. This results in substances that dissolve very freely although somewhat slowly, in water, yielding brown "colloidal solutions" which contain so few free silver ions that they do not readily precipitate chlorides or proteins. They consist of indefinite mixtures of metallic silver, silver oxide, and various silver-protein compounds, all in colloidal form. The proportions of these and the properties of the mixture vary according to the conditions under which they are produced. Although there are many gradations, most of the products on the market fall into a small number of fairly definite therapeutic groups:

- (A) Protein Silver, Strong Type.
- (B) Protein Silver, Mild Type.
- (C) Collargol Type.
- (D) Electric Type
- (E) Silver Halides

A. Protein Silver, Strong Type.—Strong protein silver compounds contain the lowest percentage of silver (from 7.5 to 8.5 per cent), but have the strongest germicidal action and are distinctly irritant. They are, therefore, therapeutically intermediate between silver nitrate and mild protein silver. Protargol belongs to this group.

Protargol is said to be prepared by precipitating a "peptone"

(albumose) solution with silver nitrate or with moist silver oxide, dissolving the silver peptonate in an excess of protal bumose, and drying *in vacuo* (Fraenkel)

B Protein Silver Mild Type—Mild protein silver compounds contain from 19 to 25 per cent of silver but are quite nonirritant. The following products listed in N N R belong to this group. Argyn Silvol Solargentum Argyn is defined as a colloidal compound of silver oxide and serum albumin. Solargentum is prepared from alkali gelatin used as a solvent for silver oxide. The solution is then concentrated and dried *in vacuo*.

C Collargol Type—This contains a much higher percentage (78) of silver said to be in the form of metallic silver reduced to the colloidal form by chemical means and stabilized by a small percentage of egg albumin with products of oxidation. However, the albumin is denatured since it does not precipitate on boiling, and it presumably constitutes the greater part of the 22 per cent that is not silver. Collargol therefore, differs from the preceding class in degree rather than in principle, containing a larger proportion of silver in the form of colloidal metal and oxide, and a smaller proportion in the form of proteinate.

D Electric Type—Metallic silver may be brought into colloidal solution electrically, i. e. by forming an arc between silver electrodes under water. These solutions are very dilute and are not sufficiently stable for concentration. They are also likely to contain silver oxide and sometimes ionized silver.

E. Silver Halides—These are mixtures of the colloidal silver salts (ten per cent of silver chloride in Lunisol 18 to 22 per cent of silver iodide in Neo Silvol) with suitable diluents. They are not astringent nor irritant and are used as mild local antiseptics. They have the advantage of being colorless.

Actions and Uses—The colloidal silver compounds are used mainly on mucous membranes for antiseptics. The strong protein silver group is most effective in this respect but is slightly irritant and stimulant. The mild protein silver group acts largely as mucilaginous demulcent and protective and as detergent, by dislodging pus. Collargol acts locally like the protein silver mild group but is used mainly to produce systemic reactions.

Eye	Strong Protein Silver	Mild Protein Silver
	Per Cent	Per Cent
Conjunctivitis simple purulent or gonorrheal	2 to 10	Solution 25 Ointment 10
Prophylaxis against ophthalmia neonatorum	2 to 10	25
Prophylaxis before ophthalmic operations (several days)		25
Corneal ulcers		50
Nose and throat	0.5 to 10	Spray 10 to 20 Swab 25 to 50
Wounds and ulcers		1 to 10 solution 10 dusting powder

Gonorrhea:		
Injections—prophylactic...	2	10
Gynecologic practice:		
Solutions	2 to 10	25 (tampons of solution in glycerin)
Tampons	2	
Ointments	5	
Suppositories	5	Suppositories, 20 (0.3 Gm)
Rectal administration:		
Injection	2	10
Suppositories	5 to 10	20 (0.13 Gm.)
Pyelography		2 (solargentum) 50 (cargentos)

The antiseptic efficiency of the silver compounds and their content of silver ions may be compared conveniently by measuring their restraining effect on gas-formation by yeast, according to the method of Dreser, as modified by Pilcher and Sollmann (*J. Lab. & Clin. Med.* 8: 301, 1923). According to this, the following solutions approximately equal the efficiency of a 1 in 1,000 solution of silver nitrate in the same media (*J. Lab. & Clin. Med.* 9: 260, 1924): Protargol in water 1 per cent, in physiological solution of sodium chloride 0.125 per cent, in blood 0.9 per cent; and Silvöl in water 36 per cent, in isotonic solution of sodium chloride 1 per cent, in blood 3 per cent.

Dosage.—The concentrations for mucous membranes range from 0.1 to 10 per cent for strong protein silver; from 5 to 50 per cent for mild protein silver, and from 0.02 to 1 per cent for collargol. These are applied every two to four hours, if possible. Solutions should be recently prepared, and should be protected against light. Ointments and suppositories are used with the same concentrations as the aqueous solutions. Stains on linen are removed by 1 in 1,000 solution of mercuric chloride. The usual concentration for special purposes are shown in the foregoing table.

Since the advent of the sulfonamide compounds and of penicillin the use of silver salts for the treatment of gonorrhea, cystitis, sinusitis and in gynecologic practice has decreased enormously. Moreover the physician using silver salts must constantly keep in mind the possibilities of later argyria. *Because of the danger of absorption and possible production of argyria, solutions of silver salts should not be used for irrigation of the bladder, of the vaginal tract, or of the intestinal tract.*

(Early Preventive) Treatment of Venereal Diseases.—The ordinary routine consists in washing the part, thoroughly with soap and water, after which a 2 per cent strong protein silver solution is injected into the urethra and held there for five minutes. The glans is then inuncted with 30 per cent mild mercurous chloride ointment for five minutes.

The efficacy has been marked if the treatment is applied thoroughly within an hour after exposure, and is fair up to three

hours In the A E F of World War I the ratio of diseases to exposure was about 1 in 30 without prophylactic treatment and 1 in 90 with treatment Prophylaxis therefore reduced the incidence to about one third (Ashburn 1919) It is practically useless after five hours

COLLOIDAL SILVER CHLORIDE N F

(HILLE LABS) —AgCl—

the presence of sucrose or

It contains not less than _____ and not more than 11 per cent of AgCl [silver chloride] —N F

For description and standards see The National Formulary under Silver Chloride Colloidal

Actions and Uses—Aqueous solutions of colloidal silver chloride have antiseptic and germicidal properties Even concentrated solutions cause neither irritation of the mucous membranes nor coagulation of albumin they do not stain the skin on topical application Possibilities of argyria from their continued use constantly must be kept in mind

Solution of colloidal silver chloride are intended for prophylaxis against and treatment of infections of the accessible mucous membranes such as the genito urinary tract and the eye ear nose and throat.

Dosage—Colloidal silver chloride is generally used in solutions In the male urethra from 3 to 25 per cent in the genito urinary tract of the female 5 to 25 per cent in inflammatory infections of the eye ear nose and throat 10 to 100 per cent in ophthalmia neonatorum 25 to 100 per cent

HILLE LABORATORIES

Liquid Lunisol An aqueous solution containing 100 Gm colloidal silver chloride in each 100 cc (1 cc of Liquid Lunisol is equivalent in silver chloride content to 1 Gm) about 84 cc — sucrose about 1 Gm —
marketed in 15
empty dilution
paring the vari
30 cc and 125 cc

Ointment Lunisol 10% Liquid Lunisol 10 cc. incorporated in 90 Gm of an unguent base composed of about 17 Gm of water 55.5 Gm of anhydrous lanolin and 27 Gm of liquid petrolatum in each hundred grams

COLLOIDAL SILVER IODIDE N F—Neo Silvol

(PARKE, DAVIS)—AgI—Silver iodide rendered colloidal stable by the presence of gelatine It contains not less than 18 per cent and not more than 22 per cent of AgI [silver iodide]

For description and standards see The National Formulary under Silver Iodide Colloidal

Actions and Uses—Colloidal silver iodide even in concen

hours, contains not less than 99.8 per cent of AgNO_3 ." U. S. P.

For description and standards see the U. S. Pharmacopeia under Silver Nitrate.

ABBOTT LABORATORIES

Solution Silver Nitrate 1% : 0.5 cc. wax ampul.

ARZOL CHEMICAL COMPANY

Applicators Silver Nitrate: Silver nitrate, 75 per cent, and potassium nitrate, 25 per cent, fused to one end of 3 inch and 6 inch wooden sticks. Each applicator is to be used but once.

PARKE, DAVIS & COMPANY

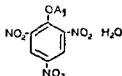
Capsules Solution Silver Nitrate, 1% : 0.4 cc. paraffin lined beeswax capsules.

U. S. patent 1,527,659 (Feb. 24, 1925; expired).

SHARP & DOHME, INC.

Solution Silver Nitrate, 1% : 0.2 cc. beeswax ampul.

SILVER PICRATE.—Picragol (WYETH).—Silver trinitrophenolate monohydrate. The structural formula may be represented as follows:



For tests and standards, see Section B.

Actions and Uses—Silver picrate has actions and uses similar to those of the other simple silver salts. Its crystals are available for making solutions of appropriate strength for use in the treatment of urethritis and infection of Bartholin's and Skene's glands by *Trichomonas vaginalis*, and *Monilia albicans* vaginitis. The aqueous solution or jelly is used in the treatment of gonococcal acute anterior urethritis and the suppositories may be used in the treatment of gonorrheal vaginitis in children. It is also used in the form of a compound powder in the treatment of vaginitis due to *Trichomonas vaginalis* and *Monilia albicans*. This compound powder contains 1 per cent silver picrate in

content and nephritis because of its picric acid content. It is therefore necessary to watch the skin for signs of argyria, and

Dosage—Dilutions of from 1 to 2 per cent are used in the form of solution compound powder and vaginal suppositories

WYETH, INCORPORATED

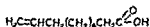
Picragol (*Crystals*): 2 Gm bottle

Picragol Compound 1% (*Powder*): Silver picrate, 1 per cent, in purified kaolin

picrate in

FUNGICIDES

ZINCUNDECATE.—Desenex (WALLACE & TIERNAN) — A preparation containing as its active ingredients undecylenic acid and zinc undecylenate. Their structural formulas may be represented as follows



Undecylenic Acid



Zinc Undecylenate

For tests and standards, see Section B under Undecylenic Acid and Zinc Undecylenate

Actions and Uses—Zincundecate is proposed for use in superficial dermatomycosis, including epidermatosis inguinale, tinea pedis, otomycosis, nomiasis, tinea corporis and tinea versicolor.

Dosage—Apply twice daily, preferably using the ointment at night, and with ambulatory patients, the powder during the day

WALLACE & TIERNAN PRODUCTS, INC

Desenex (*Powder*): 45 Gm sifter containers and 454 Gm jars. A fungicidal powder containing zinc undecylenate 20%, undecylenic acid 2% and talc U S P 78%.

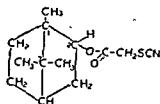
Ointment Desenex, 30 Gm tubes and 454 Gm jars. A fungicidal ointment containing zinc undecylenate 20%, undecylenic acid 5% in a water miscible base q s

U S trademark registered

PEDICULICIDES

ISOBORNYL THIOCYANOACETATE - TECHNICAL.—The technical grade of isobornyl thiocyanacetate contains 82 per cent or more of isobornyl thiocyanacetate with

other terpenes. The structural formula of isobornyl thiocyanacetate may be represented as follows:



For tests and standards, see Section B.

Actions and Uses.—Isobornyl thiocyanacetate is one of the thiocyanates shown to be effective as a pediculicide. A mixture of the technical grade of this compound with dioctyl sodium sulfosuccinate in the form of an oil emulsion is useful for external application to eradicate both the adult and ova forms of *Phthirus pubis*, *Pediculus humanus capitis* and *Pediculus hu-*

branes.

Dosage.—An oil emulsion containing isobornyl thiocyanacetate—technical 5 per cent and dioctyl sodium sulfosuccinate 0.6 per cent is applied externally in amounts of 30 to 60 cc. depending on the area involved. The emulsion is worked into a lather, of the scalp, washed with a bland soap and water. In the case of the body, the emulsion is worked well into the hair and then washed off with bland soap and water. Care must be taken that the emulsion does not remain in contact with the skin for too long a time. More than two such applications should be avoided.

WYETH INCORPORATED

Lotion Bornate: 60 cc and 3785 liter bottles. An emulsion containing isobornyl thiocyanacetate 5 per cent, dioctyl sodium sulfosuccinate 0.6 per cent in mineral oil 5 per cent gelatin 0.6 per cent and water.

PEROXIDES

Hydrogen peroxide is a combination of two atoms of hydrogen with two atoms of oxygen, one of the latter being given off to oxidizable substances, leaving a residue of water. In the presence of catalase, a ferment found in all cells, it is readily decomposed. The liberated oxygen sometimes causes considerable effervescence. For this reason it is dangerous to inject it into closed body cavities or into abscesses from which the gas has not a free exit. Hydrogen peroxide solution is official in the U. S.

Pharmacopœia This preparation is germicidal when diluted with not more than twice its volume of water. Diluted with an equal volume of water it destroys typhoid bacilli in two and one half minutes.

Metallic peroxides are compounds in which the hydrogen of hydrogen peroxide has been replaced by metals, and which are readily decomposed with liberation of hydrogen peroxide, or of oxygen.

Actions and Uses—Like hydrogen peroxide, the metallic peroxides depend for their value on the readiness with which a part of their oxygen becomes active. They are claimed to possess advantages over solution of hydrogen peroxide, because the oxygen is set free more gradually. Among themselves the metallic peroxides differ in their action in accordance with their solubility and the alkalinity produced by interaction of the peroxide with water. The action of peroxides is also affected by the nature of the metal which goes into solution when the peroxide is decomposed. Thus the use of sodium peroxide is limited by the strong base formed when it dissolves in water.

Aqueous suspensions of zinc peroxide have been found useful in the local treatment of certain wound infections such as those caused by microaerophilic or anaerobic organisms, infections caused by some aerobes, including hemolytic streptococci, have also responded to such treatment.

Because of the strong oxidizing effects on the lower organisms, the peroxides have been recommended as a convenient means of sterilizing water.

SODIUM PEROXIDE — Na_2O_2 —The sodium compound analogous to hydrogen peroxide containing at least 90 per cent of sodium peroxide.

For tests and standards, see Section B.

Actions and Uses—Sodium peroxide is not used internally, but has been used in acne, applied in the form of a paste prepared with liquid paraffin, or as a soap to remove comedones.

Metcx & Co., Inc.

Sodium Peroxide (Powder) Bulk. Contains not less than 90 per cent of sodium peroxide.

ZINC PEROXIDE MEDICINAL—U S P —"Consists of a mixture of zinc peroxide, zinc oxide and zinc hydroxide. It contains not less than 45 per cent of ZnO_2 ."—U S P.

For description and standards see The U S Pharmacopœia under Zinc Peroxide, Medicinal.

Actions and Uses—See general article Peroxides.

Dosage—Zinc peroxide medicinal (powder) sterilized in small quantities (10 to 50 Gm.) by heating in a dry oven for four hours at exactly 140°C . is made up with sterile distilled water.

to a smooth, creamy suspension of about the consistency of heavy (40 per cent) cream. The dose depends entirely on the size of the wound to be treated. Enough of the creamy suspension

MALLINCKRODT CHEMICAL WORKS

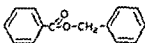
Zinc Peroxide 45% - ZnO_2 Medicinal (Powder): 30 Gm., 113 Gm. and 453 Gm bottles.

MERCK & CO., INC.

Zinc Peroxide-Special Medicinal (Powder): 15 Gm., 30 Gm., 113 Gm and 453 Gm bottles

SCABICIDES

BENZYL BENZOATE U. S. P.—Benylate (Breon).— $\text{C}_{14}\text{H}_{12}\text{O}_2$ —A clear, colorless oily liquid with slight aromatic odor employed externally in various emulsions containing 25 to 30 per cent. The structural formula for benzyl benzoate may be represented as follows.



For standards, see U. S. Pharmacopeia under Benzyl Benzoate and Benzyl Benzoate Lotion.

Actions and Uses.—Benzyl benzoate applied externally in the form of a 25 to 30 per cent emulsion or lotion has been found to be an effective scabicide. Although reported to be somewhat effective also as a pediculicide, its use for pediculosis uncomplicated by scabies is not recommended. Application is occasionally followed by a slight, transitory burning sensation. Rarely, severe skin irritation may occur in patients with particularly sensitive skins. It should never be allowed to come in contact with the eyes.

Dosage.—A 25 to 30 per cent lotion or emulsion of benzyl benzoate is applied with a swab or brush over the entire body surface (except the face) while the skin is still damp immediately following scrubbing of the lesions in a 10-minute soap-warm water bath. Care should be taken to insure application to and around the nails. The first application is allowed to dry and a

second application made to the most involved areas. Children ordinarily require 60 cc. to 90 cc. and adults 120 cc. to 180 cc. for a single treatment. Adequate sterilization of bed and body in clothing is required treatment necessary to do not contact measures

GEORGE A. BREON AND COMPANY

Lotion Benylate: 120 cc., 480 cc. and 3,840 cc. bottles. An oil in water emulsion containing 25 per cent of benzyl benzoate and approximately 2 per cent of triethanolamine stearate. The product is required to be labeled as Modified Benzyl Benzoate Lotion because it differs from the official benzyl benzoate lotion, U. S. P., essentially by the emulsifying agent used in its preparation.

base.

For tests and standards, see Section B.

Actions and Uses—Pyrethrum ointment—Upsher Smith has

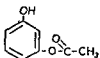
treated, while Sweitzer found only one case of sensitivity (after three months' use) in 595 additional cases.

UPSHER SMITH COMPANY

Ointment Pyrethrum: 100 Gm. and 2.7 Kg. containers

RESORCIN COMPOUNDS

RESORCINOL MONOACETATE—N. F.—Euresol (BILHUBER-KNOLL.)—*m*-Hydroxyphenyl Acetate.—The structural formula may be represented as follows:



For description and standards see The National Formulary under Resorcinol Monoacetate.

Actions and Uses.—The action of resorcinol monoacetate is similar to that of resorcinol, but milder and more lasting because of the gradual liberation of resorcinol. Moreover, resorcinol monoacetate in contrast to resorcin does not give a greenish tint to light or gray hair.

Resorcinol monoacetate is used as an adjuvant in the treatment of acne, of sycosis vulgaris, of alopecia and of seborrhea.

Dosage—Resorcinol monoacetate is applied in ointments of from 5 to 20 per cent and in acetone solution. For scalp lotions, alcohol solutions of from 3 to 5 per cent of resorcinol monoacetate are used.

BILHUBER-KNOLL CORP

Euresol pro Capillis (Powder): Resorcinol monoacetate with isopropyl alcohol 6 per cent, perfumed to render it suitable for scalp lotions, supplied in 30 Gm. and 240 Gm. bottles

U. S. trademark 88,894.

EASTMAN KODAK COMPANY

Resorcinol Monoacetate (Liquid): Bulk.

SULFOICHTHYOLATE PREPARATIONS AND SUBSTITUTES

Preparations containing as their essential constituents salts or compounds of a mixture of acids containing sulfur and designated by the group name "sulfoichthyolic acid" are obtained from certain bitumins characterized by a high content of sulfur in the form of sulfon compounds of this sort as ichthyol—has been associated with sodium and other metals and have also been introduced.

A number of more or less related compounds of sulfur have been introduced as substitutes for the sulfoichthyolates; and the National Formulary contains a sulfoichthyolate preparation under the title, "Ichthammol."

Actions and Uses—The current estimate of the effects of sulfoichthyolic acid preparations is based largely on the use of ichthyol. The use of sulfoichthyolate preparations is still largely empiric. They are weakly antiseptic and emollient. Taken internally, they produce some gastro intestinal irritation, with diarrhea etc.

They were formerly used locally under the supposition that they secure the absorption of swellings and effusions in contusions, burns, etc., and especially in gynecologic practice, and in various skin diseases. They have been tried internally in a great variety of conditions, but there is no evidence that they are of any therapeutic value when used in this way.

Systemic Anti-Infectives

Systemic anti-infectives are broadly classified to include therapeutic agents administered internally, either orally or parenterally, against infection in its broadest sense. Thus the chapter includes antibacterial, antibiotic, antimalarial antiprotozoan, antirickettsial and anthelmintic drugs as well as those effective in certain virus and fungus diseases. Some of the anthelmintics and the so-called urinary or intestinal antiseptics, though used principally for their local effect, are included because they are administered internally. Others that may be used, both locally and internally, are included in this or the chapter on Local Anti-Infectives on the basis of the principal method of application, as nearly as this can be determined.

The inhibitory effect of *para*-aminobenzoic acid upon sulfonamide activity is frequently effectively utilized in blood or other cultures to isolate bacterial infection in patients already under treatment with a sulfonamide compound. It should therefore be borne in mind that agents possessing a *para*-aminobenzoyl group as part of their chemical structure, notably procaine and related local anesthetics, are capable of inhibiting the activity of sulfonamides, especially when the latter are administered to control infection in a specific region that is the site of local anesthesia for surgical intervention

ANTIBACTERIAL AGENTS

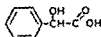
Chaulmoogra Derivatives

Chaulmoogra Oil and ethyl chaulmoograte are described in The National Formulary. Chaulmoogra oil has been used in the treatment of leprosy for many years. The evidence behind this use indicated that it might be of possible value, though not having specific curative properties. However, experienced observers consider the oil and its derivatives valueless in the treatment of leprosy. Further, cases for treatment with this drug and its derivatives must be selected with great care or much harm may be done. The Council on Pharmacy and Chemistry has given consideration to the status of these agents and is of the opinion that the evidence now available does not support claims for the use of chaulmoogra oil and its derivatives for the treatment of leprosy. However, ethyl chaulmoograte is reported to have been

found to be of definite value in sarcoidosis (Schaumann's Disease) formerly spoken of as Boeck's Sarcoid

Mandelic Acid Derivatives

MANDELIC ACID-N F—Racemic Mandelic Acid—
'When dried over sulfuric acid for 18 hours contains not less than 99 per cent of $\text{HC}_8\text{H}_7\text{O}_3$ N F Mandelic acid has the following structural formula



For description and standards see The National Formulary under Mandelic Acid.

Actions and Uses—Mandelic acid is a nonmetabolizable substance which when administered by mouth is excreted unchanged in the urine, and if the pH of the urine is kept at 5.5 or less it is rendered bactericidal or bacteriostatic against *Escherichia coli*, *Aerobacter aerogenes*, *Streptococcus faecalis* and organisms of the *Proteus*, *Pseudomonas*, *Alcaligenes*, *Salmonella* and *Shigella* groups. The acidity should be controlled by frequent determinations of the pH. In cases in which the acidity is not reduced to pH 5.5 or less other acidifying agents such as ammonium chloride, ammonium nitrate or nitrohydrochloric acid may be administered concurrently providing there are no contraindications. For the same purpose the ketogenic diet has also been employed. Fluid intake should be restricted to an amount not exceeding 1,200 cc. daily. It is usually neither necessary nor advisable to continue mandelic acid therapy longer than from twelve to fourteen days, as renal irritation may ensue. Nausea, diarrhea, dysuria and hematuria may also occur occasionally, requiring reduction in dosage or interruption of therapy. Mandelic acid should not be administered in the presence of renal insufficiency as an inadequate concentration is obtained in the urine, renal irritation may result, and serious acidosis may occur from retention of the acid.

Dosage—The usual dosage is 3 Gm. four times a day either as the free acid or in the form of the sodium or ammonium salt. An additional acidifying agent is usually required when the sodium salt is employed.

GANE AND INGRAM INC.

Mandelic Acid (Powder) Bulk

MALLINCKRODT CHEMICAL WORKS

Mandelic Acid (Powder) Bulk

MERCK & CO. INC.

Mandelic Acid (Powder) Bulk.

sulfapyrazine are the drugs of choice, with sulfanilamide second, and sulfathiazole third. Pneumococcic infections are best treated with sulfadiazine or sulfamerazine. Sulfathiazole is the second drug of choice in these infections. On the basis of existing evidence sulfathiazole or sulfadiazine are the drugs of choice in the treatment of gonococcic infections. Sulfadiazine, sulfamerazine or sulfathiazole is the drug of choice in the treatment of staphylococcic infections. Meningococcic infections respond well to therapy with sulfadiazine, sulfamerazine, sulfapyrazine, sulfathiazole or sulfanilamide, but current evidence indicates that sulfadiazine and sulfamerazine are the drugs of choice. Sulfadiazine is indicated for use in Friedländer's bacillus infections, with sulfathiazole second. *Shigella dysenteriae* and *H. influenzae* infections are among those most likely to respond to sulfadiazine therapy. Recently a number of authors have proposed the oral administration of sulfadiazine for the treatment of gonococcal ophthalmia. It is believed that such use of sulfonamides shortens the period of active infection and diminishes the likelihood of ophthalmic complications.

The clinical evidence as to the effectiveness of sulfonamide compounds in the control of alpha-hemolytic streptococcus infections, is not completely clear. In tissue infections (other than subacute bacterial endocarditis) produced by the so-called "mouth varieties" of the organism, sulfadiazine or sulfathiazole seem to be about equally effective. None of the sulfonamides are active against the enterococcus group of streptococci. Sulfathiazole is the drug of choice in the treatment of chancroid. Acute bacillary dysentery responds well to sulfadiazine, sulfathiazole, sulfaguanidine. Sulfadiazine should, on the basis of actinomycosis. In general, urinary tract infections respond best to the sulfonamide drugs which are recommended for use in tissue infections produced by the same organism. Anaerobic streptococcus infections, regardless of their location, do not respond to sulfonamide therapy.

While reports of the definite clinical efficacy of the sulfonamide compounds are extant in respect to hemolytic streptococci Groups B and C, *Brucella melitensis*, *Pasteurella tularensis*, *Clostridium perfringens*, *Clostridium septicum*, *Hemophilus influenzae* and certain other bacterial infections, definite experimental and clinical data which would justify the selection of drugs of choice in infections caused by these organisms are not available at the present time, and the treatment of disease produced by these organisms with the sulfonamides must be regarded still as being problems of clinical investigation.

Four diseases of probable viral etiology.

Follicular
con-
which
vari-
able.
in the

therapeutic use of sulfanilamide, sulfathiazole or sulfadiazine. Further, while some cases of molluscum contagiosum no doubt respond to sulfonamide therapy, other less potent medicaments which may be applied locally offer equal therapeutic results.

Sulfadiazine has been demonstrated as an effective agent

it unsatisfactory for general systemic use

or active phase of rheumatic fever

At the present time the Council feels that the evidence for the peroral prophylactic use of sulfonamides in rheumatic fever and for the prevention of pneumonia and other complications of common colds, influenza or measles is unclear, and their use should not be generally recommended.

Laboratory studies have shown that the sulfonamides may be bound to plasma protein, the percentage of binding varying with the drugs, apparently being lowest for sulfanilamide (about 20 per cent) and highest with sulfamerazine (about 80 to 85 per cent), sulfapyrazine and sulfathiazole may show binding as high as 50 and 75 per cent respectively. These studies have raised a question whether such binding makes the sulfonamide ineffective as an anti-infective agent. The available evidence indicates that the protein does not truly inactivate the sulfonamide. It should be remembered that even when the sulfonamides are bound to proteins in the blood they are gradually released with the passage of time. Thus even though one of two compared sulfonamide compounds may have a greater tendency to bind with the plasma protein, any differences in therapeutic effects cannot be attributed solely to such protein binding.

Experience gained in World War II seems to indicate that the use of crystalline sulfonamides and of sulfonamide ointments, creams, lotions, etc. as topical agents was not very successful in

Fluids—It is
ie sulfonamides
by the method
hem 128 537,

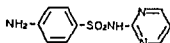
[May] 1939)

Since the dosages suggested below are based on body weight

SULFADIAZINE-U. S

2-Sulfanilylaminopyrimidine,
sulfonamide—"When dried
not less than 99 per cent of

Sulfadiazine has the following structural formula:



For description and standards see the U. S. Pharmacopeia under Sulfadiazine and Sulfadiazine Tablets

tract is slower and, in general, less complete than that of sulfathiazole or sulfanilamide. Sulfadiazine is, as a rule, *conjugated* to the acetylated form in a lesser degree in the blood and tissues than is sulfanilamide or sulfathiazole. It does not pass into the body water as readily as does sulfathiazole or sulfanilamide, but it does pass into the cerebrospinal fluid in about the same manner as does sulfanilamide. The drug passes into pleural and abdominal fluids in concentrations of one half to four fifths of those noted in the blood and penetrates the red cells with ease.

It is excreted quite readily by the kidneys, in respect both to the drug itself and to its acetylated fraction. Relatively high concentrations of sulfadiazine are easily obtained in the blood of patients to whom the drug is administered, because it is not evenly distributed in the tissues of the body. If kidney function is impaired, the excretion of sulfadiazine will be reduced and the drug will accumulate in the blood and tissues. The excretion of the drug is generally complete within 48 hours after the administration of a single dose of the compound, and in the urine less sulfadiazine is found in the conjugated form than has been noted with sulfanilamide or sulfathiazole.

The toxic manifestations noted in the course of sulfadiazine therapy are similar to those noted previously in the course of therapy with the other sulfonamide drugs. They are generally unpredictable in their occurrence and are generally the result of an idiosyncrasy to the drug.

Sulfadiazine causes fewer toxic reactions than do sulfanilamide or sulfathiazole. Nausea, vomiting and dizziness are uncommon. Mental disturbances and psychoses have been described. Peripheral neuritis has not been reported. Cyanosis is rare and acidosis does not occur. Fever and rashes due to the drug are less common than with the other sulfonamide drugs, except *sulfaguanidine*. Patients receiving sulfadiazine should be kept out of the sun. Injection of the conjunctivas and scleras has been noted. Hepatitis has been rare, but leukopenia with granulocytopenia has been observed early and late in the course of the therapy. Acute agranulocytosis has been noted rarely, occurring

during the third week or later of therapy with this drug. Severe hemolytic anemias are rare. Microscopic and gross hematuria have been noted and oliguria and anuria with azotemia have

Dosage—Sulfadiazine is poorly soluble and hence must be administered by the oral route. In adults suffering from pneumococcal pneumonia, severe hemolytic streptococcus infections, severe staphylococcal infections or meningococcal meningitis, the initial dose should be based on 0.10 Gm. per kilogram of body weight. Then if the patient is suffering from pneumococcal pneumonia, 1.0 Gm. should be given every four hours day and night until the temperature has been normal for seventy-two hours. The drug may then be stopped. In severe streptococcal, staphylococcal and meningococcal infections, subsequent doses after the initial doses is 1.0 to 1.5 Gm. every four hours day and night until the temperature has been normal for from five to seven days. At this time the drug may be either stopped or continued in smaller doses until the complete recovery of the patient is assured.

In children suffering from pneumonia, the initial oral dose should be based on 0.10 to 0.15 Gm. per kilogram of body weight and subsequent doses should be one fourth of the initial dose given at intervals of six hours until the temperature has been normal for at least forty-eight hours. In severe streptococcal,

In mild or moderately severe hemolytic streptococcus infections, an initial oral dose of 0.05 Gm. per kilogram of body weight followed by one third of the initial dose given every four hours day and night by mouth until the temperature has been normal for three to five days has been suggested as a satisfactory dosage schedule. All of the above dosages should be controlled if possible by determination of the concentration of the drug in the blood at frequent intervals (see Bratton and Marshall method under Determination of the Sulfonamides in Body Fluids). In severe streptococcal, staphylococcal, meningococcal or Friedlander's bacillus infections it is necessary during the febrile period to obtain and maintain concentrations of approximately 15 mg. of sulfadiazine per hundred cubic centi

meters in the blood of the patients. It is rarely necessary or advisable to attempt knowingly to exceed this concentration of

The incidence of oliguria, hematuria and anuria following sulfadiazine therapy may prove to be great under conditions where the output of urine cannot be maintained above 600 or 800 cc. per day, as in tropical climates or where a shortage of water exists. It is recommended that under conditions where such complications are being encountered the medical officers shall administer an initial dose of 4 grams of sodium bicarbonate together with an initial dose of sulfadiazine, and shall follow this with 2 grams of sodium bicarbonate every four hours regardless of the management of sulfadiazine. Doses of alkali, such as 3 or 4 grams every four hours, may be helpful.

ABBOTT LABORATORIES

Sulfadiazine Sodium (*Sterile Powder*): 5 Gm. ampuls.

Tablets Sulfadiazine: 0.5 Gm.

AMERICAN PHARMACEUTICAL CO., INC.

Tablets Sulfadiazine: 0.5 Gm.

BUFFINGTON'S, INC.

Tablets Sulfadiazine: 0.5 Gm.

COLE CHEMICAL CO.

Tablets Sulfadiazine: 0.5 Gm.

FLINT, EATON & Co.

Tablets Sulfadiazine: 0.5 Gm.

THE HARROWER LABORATORY, INC.

Tablets Sulfadiazine: 0.5 Gm.

LEDERLE LABORATORIES, DIVISION AMERICAN CYANAMID CO.

Sulfadiazine (*Powder*): 113 Gm. and 454 Gm. packages.

Tablets Sulfadiazine: 0.5 Gm.

ELI LILLY & Co.

Tablets Sulfadiazine: 65 mg. and 0.5 Gm.

MCNEIL LABORATORIES

Liquoid Sulfadiazine: 120 cc. and 480 cc. bottles.

Tablets Sulfadiazine: 0.5 Gm

THE WM S MERRILL COMPANY

Tablets Sulfadiazine: 0.5 Gm

E. S. MILLER LABORATORIES, INC.

Tablets Sulfadiazine: 0.5 Gm

PARKE, DAVIS & COMPANY

Tablets Sulfadiazine: 0.5 Gm

PITMAN-MOORE

Solution Magmoid Sulfadiazine: 30 cc., 60 cc., 360 cc. and 384 liter bottles Preserved with benzoic acid 0.25 per cent

WILLIAM H. RORER, INC.

Tablets Sulfadiazine: 0.5 Gm

SHARP & DOHME, INC

Tablets Sulfadiazine: 0.5 Gm

CARROLL DUNHAM SMITH PHARMACEUTICAL CO

Sulfadiazine Tablets: 0.5 Gm

SMITH-DORSEY COMPANY

Tablets Sulfadiazine: 0.1 Gm and 0.5 Gm.

E. R. SQUIBB & SONS

Tablets Sulfadiazine: 0.5 Gm

THE UPJOHN COMPANY

Tablets Sulfadiazine: 0.5 Gm

THE VALE CHEMICAL CO., INC

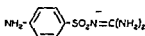
Tablets Sulfadiazine: 0.5 Gm.

WINTHROP-STEARNES, INC.

Tablets Sulfadiazine: 0.5 Gm

— — — — —
 dylguanidine mono-
 monohydrate. —
 contains not less than

Sulfaguanidine has the following structural formula:



For description and standards see the U. S. Pharmacopeia under Sulfaguanidine and Sulfaguanidine Tablets

Actions and Uses.—The development of sulfaguanidine represented a new concept in bacterial chemotherapy, namely that a sulfonamide drug could be given by mouth and be quite soluble in the intestinal contents, while at the same time it would be poorly absorbed from the gastrointestinal tract, thus permitting the drug to exert its bacteriostatic and bactericidal action locally in the gastrointestinal tract.

The proper use of this drug demands that the physician shall use optimal doses spaced at such intervals as will give rise to high concentration of the drug in the stool with possibilities for minimal absorption from the gastrointestinal tract. In actual practice, one finds that when the drug is properly administered the concentrations of sulfaguanidine in the blood rarely exceed 5 mg per hundred cubic centimeters.

On the basis of accumulated evidence the Council recognizes claims for the prophylactic use of sulfaguanidine as well as other sulfonamides in dysentery.

Sulfaguanidine is one of the least toxic of all commonly used sulfonamide drugs but nausea with vomiting, drug rash, drug fever and other types of idiosyncrasy are not uncommon. If toxic reactions occur, the drug should be stopped and fluids forced, and enemas given to eliminate the drug from the body as soon as possible.

Dosage.—In bacillary dysentery the initial dose by mouth is 0.05 Gm. per kilogram of body weight followed by a main-
four hours day and
or less daily; then
at least three days.
days it is unlikely
administration. It is
generally not considered wise to continue the drug for a period
of more than fourteen days

When sulfaguanidine is being used as a prophylactic agent prior to operations on the colon, the recommended dosage is 0.05 Gm. per kilogram of body weight by mouth every eight hours day and night for five days before the operation. Then, as soon as possible after the operation, the drug should be started by mouth in the same dosage and continued for seven days. It is not, as a rule, necessary to continue the drug longer. It is recommended that the total period of dosage should not exceed fourteen days.

LEDERLE LABORATORIES, DIVISION AMERICAN CYANAMID CO.

Sulfaguanidine (Unsterile Powder): Bulk.

Tablets Sulfaguanidine: 0.5 Gm

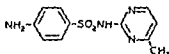
E. R. SQUIBB & SONS

Tablets Sulfaguanidine: 0.5 Gm.

SULFAMERAZINE-U. S. P.—Sulfamethyldiazine — 4-Methyl-2-sulfanilamidopyrimidine — 4-Methyl-2-sulfanilylamino-

pyrimidine — *p* Amino-N-2-(4 methylpyrimidyl)benzenesulfonamide — "When dried at 100 C. for 4 hours contains not less than 99 per cent of $C_{11}H_{11}N_4O_2S$ " — U S P

Sulfamerazine has the following structural formula



For description and standards see the U S Pharmacopeia under Sulfamerazine and Sulfamerazine Tablets

Actions and Uses — The oral administration of equal doses

more completely absorbed from the gastrointestinal tract but is excreted more slowly than sulfadiazine. Thus it may be given in smaller amounts and less frequently. This drug penetrates cerebrospinal pleura and peritoneal fluids. The concentration of free drug in cerebrospinal fluid is approximately 50 per cent of that in serum.

The next best form of sulfamerazine is more soluble than

tions of the drug are maintained. Animal experiments suggest that the two drugs otherwise have about the same degree of toxicity but further clinical investigations in humans remain to be done to reveal the true toxicity status of sulfamerazine.

Sulfamerazine may be used in the treatment of pneumococcal streptococcal meningococcal and gonococcal infections.

Dosage — In the treatment of acute pneumococcal, streptococcal, meningococcal, and gonococcal infections, a dose of 5 mg of the drug per kg of body weight, given four times a day, within four hours after the onset of symptoms, is recommended.

temperature, pulse and respiration rates return to normal.

For infants under six months of age, 0.5 Gm initial dose and 0.25 Gm every twelve hours thereafter; infants six months to

In the treatment of pneumococcic infections, type-specific antiserum may be administered, unless contraindicated, if the response of the patient to the drug alone is not adequate within 18 to 24 hours.

As in the case of the other sulfonamides, the appearance of toxic symptoms should be an indication for the cessation of all treatment with this drug.

ABBOTT LABORATORIES

Tablets Sulfamerazine: 0.5 Gm.

AMERICAN PHARMACEUTICAL COMPANY, INC.

Tablets Sulfamerazine: 0.5 Gm.

LEDERLE LABORATORIES, DIVISION AMERICAN CYANAMID CO.

Sulfamerazine (*Unsterile Powder*): 113 Gm. and 454 Gm. packages.

Tablets Sulfamerazine: 0.5 Gm.

ELI LILLY & CO.

Tablets Sulfamerazine: 0.5 Gm.

S. E. MASSENGILL CO.

Tablets Sulfamerazine: 0.5 Gm.

PARKE, DAVIS & COMPANY

Tablets Sulfamerazine: 0.5 Gm.

SHARP & DOHME, INC.

Sulfamerazine (*Unsterile Powder*): 120 Gm. and 480 Gm. containers.

Sulfamerazine Chemical Reagent (*Powder*): 1 Gm. vial

Tablets Sulfamerazine: 0.5 Gm.

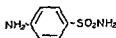
E. R. SQUIBB & SONS

Tablets Sulfamerazine: 0.5 Gm.

THE UPJOHN COMPANY

Tablets Sulfamerazine: 0.5 Gm.

SULFANILAMIDE-U. S. P. — *p*-Amino benzene sulfonamide—The amide of sulfanilic acid "When dried at 100 C for 4 hours, contains not less than 99 per cent of $C_6H_5O_2N_2S$." U. S. P. Sulfanilamide has the following structural formula:



For description and standards see the U. S. Pharmacopeia under Sulfanilamide and Sulfanilamide Tablets.

Actions and Uses—Sulfanilamide when administered by mouth is readily absorbed from the gastrointestinal tract. It is probable that, following a single peroral dose, absorption is practically complete within four hours. The drug is evenly distributed in all body tissues with the exception of the brain, fat and bone. In patients with normal renal function, from 10 to 20 per cent of the circulating sulfanilamide is present in the acetylated or conjugated form. The drug is almost totally absorbed and is readily excreted by the normal kidneys. In the urine ordinarily from one third to one half of the excreted sulfanilamide exists as the acetylated fraction.

Many patients receiving sulfanilamide will have signs and symptoms of central nervous system disturbances such as headache, dizziness, nausea, vomiting, mild depressions or elations and in a few instances, severe toxic psychoses. Because of these toxic manifestations, patients who are receiving the drug should be warned against driving automobiles, piloting or riding in airplanes and doing any heavy or dangerous work in which a spell of dizziness might result in a serious accident. Practically all individuals who receive therapeutic doses of the drug develop some degree of cyanosis generally apparent in the lips and nail beds, but in some cases suffusing the entire integument. The exact mode of production of this cyanosis is unknown, although in many instances it is due, at least in part, to the production of methemoglobin in the blood. It is not, in the opinion of most observers, a serious complication and rarely serves as an indication that treatment should be discontinued. Drug fever, which commonly occurs between the fifth and ninth days of therapy, is a not infrequent toxic manifestation. Rashes, which may vary in their type and which may be accompanied by fever, are also not infrequently seen in the course of sulfanilamide therapy. As these rashes are sometimes the result of a photosensitization of the skin, it is probably best for patients who are receiving sulfanilamide to keep out of the sun and they should not receive ultraviolet irradiation.

Acidosis may be produced by the drug in certain individuals. This is probably brought about by the action of sulfanilamide in inhibiting the enzyme carbonic anhydrase. The routine, concurrent use of sodium bicarbonate generally prevents this complication of drug therapy. Hepatitis, accompanied by jaundice and, in a few instances, ending fatally, is one of the rarer complications of sulfanilamide therapy. Acute hemolytic anemia occurring from the first to the twenty first day of therapy, is not uncommon and is noted more frequently in Negro patients than in white patients. A severe leukopenia may occur at any time during the course of therapy, and granulocytopenia has been described not uncommonly as a toxic manifestation. The most common time for the appearance of true agranulocytosis is between the four-blood cell counts should be done at least every two days. In tenth and fortieth days of therapy. During this period white patients who have a decrease in renal function the normal excretion of the drug is impaired, and an accumulation of

sulfanilamide in the blood and tissues of the patient may occur if care is not taken in regulating the dosage of the drug.

As far as is known, practically all other drugs may be prescribed concurrently with sulfanilamide.

Dosage.—The dose of sulfanilamide depends on the type and severity of the infection. It is suggested that in cases of serious infection an initial peroral dose of 0.1 Gm. per kilogram of body weight be administered, this to be followed by doses of the drug of one-sixth the amount of the initial dose given at four hour intervals day and night until the temperature has been normal for seventy-two hours. Then the dose of the drug may be gradually decreased until complete convalescence is established.

It is usually advisable to continue therapy for a few days after clinical recovery has taken place in order to avoid relapses. Patients who cannot take the drug by mouth may be given subcutaneous injections of a 1 per cent solution of sulfanilamide made up in isotonic solutions of sodium chloride or, better still, in one-sixth molar sodium racemic lactate solutions. The same total dosage may be employed for parenteral as for oral administration, but the injections should be given at intervals of from six to eight hours.

ABBOTT LABORATORIES

Sulfanilamide (*Crystals*): 1.0 Gm. and 4.0 Gm. ampuls.

Tablets Sulfanilamide: 0.324 Gm. and 0.5 Gm.

AMERICAN PHARMACEUTICAL Co., INC.

Sulfanilamide (*Powder*): 113.4 Gm. and 453.6 Gm. packages.

Tablets Sulfanilamide: 0.324 Gm. and 0.486 Gm.

CIBA PHARMACEUTICAL PRODUCTS, INC.

Tablets Sulfanilamide: 0.5 Gm.

THE DRUG PRODUCTS Co., INC.

Pulvoids Sulfanilamide: 0.324 Gm.

ENDO PRODUCTS, INC.

Tablets Sulfanilamide: 0.324 Gm. and 0.5 Gm.

FLINT, EATON & COMPANY

Tablets Sulfanilamide: 65 mg., 0.25 Gm., 0.324 Gm. and 0.5 Gm.

GANE AND INGRAM, INC.

Sulfanilamide (*Powder*): Bulk.

Horton & Converse

Tablets Sulfanilamide: 0.324 Gm.

LYDERLE LABORATORIES, DIVISION AMERICAN CYANAMID CO.

Sulfanilamide (*Unsterile Powder*) • 113 Gm. and 454 Gm. packages

THE MALTIF CHEMICAL COMPANY

Tablets Sulfanilamide: 0.324 Gm

MEYER & CO., INC.

Sulfanilamide (Powder): Bulk

THE W & S MERRILL COMPANY

Tablets Sulfanilamide: 0.324 Gm.

E. S. MILLER LABORATORIES, INC.

Tablets Sulfanilamide, 0.324 Gm.

NATIONAL DRUG COMPANY

Tablets Sulfanilamide • 0.325 Gm

PARKE, DAVIS & COMPANY

Tablets Sulfanilamide, 0.324 Gm. and 0.5 Gm.

PRUMAN-MCCOY CO., DIVISION OF ALLIED LABORATORIES, INC.

Tablets Sulfanilamide 0.24 Gm

SCHMITZLIN & Co.

Tablets Sulfanilamide • 0.5 Gm.

SHARP & DOWNE, INC.

Tablets Sulfanilamide- 0.324 Gm. and 0.5 Gm.

CARRILL DUNHAM SMITH PHARMACEUTICAL CO.

Tablets Sulfanilamide 0.124 Gm

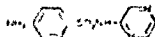
THE URBAN COMPANY

Tablets Sulfanilamide (5 mg and 0.5 Gm)

[illegible]

Tablets Sulfanilamide • 0.5 (gr)

SULFAPYRAZINE - 2 S. for 1 am + pyrazine = 2 S. for 1
 pyrazine + pyrazine = 2 S. for 1 am + 2 pyrazine (pyrazine)
 2 - pyrazine has 1 of "new" structural formula



For tests and standards, see Section II.

[illegible]

of toxicity in experimental animals. Although renal damage has

been observed with single large oral doses of one gram every

Sulfapyrazine is probably as effective as sulfadiazine in the treatment of pneumococcal, hemolytic streptococcal and *B. coli* infections. Further it appears to be effective against *Shigella paradysenteriae*, even when these strains are resistant to other sulfonamides, and in the presence of meningococcic meningitis.

Dosage.—Low blood levels commonly follow administration of sulfapyrazine and often are effective. The usual dosage, however, produces concentrations from 5 to 12 mg. per 100 cc. of blood.

Initial dose for adults is 2 to 4 grams, followed by 1 gram doses at four to six hour intervals. Treatment should be continued until the temperature, pulse and respiration have been normal for three days. Infants and children should receive about 130 mg. of the drug per kilo of body weight. In general, infants under six months of age may receive 0.5 Gm. as an initial dose and 0.25 Gm. every six hours thereafter; children six months to three years, 1.0 gram initial dose, 0.5 Gm. every six hours; children three to ten years, 2.0 Gm. initial dose and 1.0 Gm. every six hours. In very severe infections the dose may be increased by 50 per cent.

MEAD JOHNSON & COMPANY

Tablets Sulfapyrazine: 0.5 Gm.

U. S. patent 2,420,703.

Sulfonamide Sodium Salts

Clinical Pharmacology.—Solutions of sulfonamide sodium salts in distilled water are strongly alkaline and have pH ranges of from 9 to 11. When solutions of these drugs are injected intravenously the sodium ions are promptly split off, leaving the sulfonamide compound in the circulating blood. Hence, in the

sulfonamide sodium salts represent vehicles for
the body.
Its of sul-
5 per cent
lium chlo-

The administration of 5 per cent solutions of the sodium salts of the sulfonamide compounds by the intravenous route should be carried out carefully because these solutions, being highly alkaline, are definitely irritating to the tissues and, if they are permitted to leak outside the vein may cause necrosis of the

isotonic Ringer's solution by the subcutaneous route. However, the general use of this route is not advised unless the drugs cannot be administered by the intravenous route.

Action and Effect.—The following are the results of the

blood and tissues by other routes of administration

With the exception of patients ill with severe infections, or those individuals to whom these drugs cannot be given by the oral route, it is rarely necessary to administer intravenous in-

tonamide compounds by the parenteral route, administration of the parent drug should be commenced by the oral route.

Toxicity.—Aside from the damage to tissues which may re-

SULFADIAZINE SODIUM—U. S. P.—The sodium salt of 2-sulfanilamidopyrimidine—"When dried at 105° C. for 4 hours, contains not less than 99 per cent of $C_{10}H_9N_4O_2SNa$."—**U. S. P.**

For description and standards see The U. S. Pharmacopeia under Sulfadiazine Sodium

Actions and Uses.—The sodium salt of sulfadiazine has the same therapeutic activities and properties as does sulfadiazine. This compound has proved to be of value in the treatment of severe hemolytic streptococcus, pneumococcic, meningococcic, staphylococcic and *Escherichia coli* tissue infections.

Dosage.—The usual initial dose of this drug for patients who are severely ill with infections which are susceptible to the therapeutic effects of this drug is based on 0.10 gram per kilogram of body weight, up to 50 Kg. of body weight, this being made up as a 5 per cent solution in sterile distilled water or isotonic solution of sodium chloride. Regardless of the weight of the patient, it is best not to exceed a total initial dosage of 5.0 gram of sulfadiazine sodium.

It is always advisable to attempt to continue therapy by the same route, but, if this is not possible, the drug should be given by the intravenous route. The dose should be 0.10 gram per kilogram of body weight, made up in a 5 per cent solution in distilled water.

well as adults.

LEDERLE LABORATORIES, DIVISION AMERICAN CYANAMID CO.

Sodium Sulfadiazine (Sterile Powder): 5 Gm. vials. Each

SHARP & DOHME, INC.

Solution Sodium Sulfadiazine 5%: 50 cc. ampuls. Each 50 cubic centimeters contains sodium sulfadiazine 2.5 Gm. and distilled water q. s.

The following brands conform to the Sterile Sulfadiazine Sodium-U. S. P.:

SHARP & DOHME, INC.

Sodium Sulfadiazine (Sterile Powder): 5 Gm. vials.

E. R. SQUIBB & SONS

Sodium Sulfadiazine (Sterile Powder): 5 Gm. vials

For description and standards see The U. S. Pharmacopeia under Sulfamerazine Sodium.

Actions and Uses—Sodium sulfamerazine may be used intravenously for critically ill patients who require immediate and

factory drug level can be maintained by oral administration.

Dosage—The initial dose of sulfamerazine sodium for patients

is 0.5 g. per kg. body weight, this being made up as a 5 per cent solution in sterile distilled water or sterile isotonic solution of sodium chloride. It is possible to attempt to

chloride and administered by the intravenous route at intervals

LEDERLE LABORATORIES, DIVISION AMERICAN CYANAMID CO.

Solution Sodium Sulfamerazine 25%: 10 cc. ampuls

SHARP & DOHME, INC.

Sodium Sulfamerazine (Sterile Powder): 5 Gm. vial

Solution Sodium Sulfamerazine 6%: 50 cc ampules Each 50 cc. contains sodium sulfamerazine 3 Gm. in distilled water.

SULFAPYRAZINE SODIUM.—The monohydrated sodium salt of 2 sulfanilamidopyrazine

For tests and standards, see Section B

Actions and Uses—Sodium sulfapyrazine may be administered intravenously when oral administration of sulfapyrazine is not feasible or when there is a need for a more rapid effect. It may be given by the intramuscular route, but this should be avoided if possible.

This drug should not be injected intramuscularly or intraspinally.

Dosage—The initial dosage of sulfapyrazine sodium for patients who are severely ill with infections which are susceptible to the therapeutic effects of this drug is based upon 0.05 gram per kilogram of body weight, this being made up as a 5 per cent solution in sterile distilled water or sterile isotonic solution of sodium chloride. If subsequent doses of sulfapyrazine

sodium are desirable, they should be based on 0.025 gram of sulfapyrazine sodium per kilogram of body weight made up as a 5 per cent solution in sterile distilled water or sterile isotonic solution of sodium chloride and administered by the intravenous route at intervals of the concentration of the concentrations of the drug per cent are undesired dosage should be reduced.

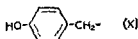
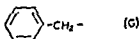
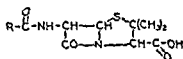
MEAD JOHNSON & COMPANY

Sodium Sulfapyrazine (Powder): 5 Gm. bottles.

ANTIBIOTICS

Penicillin

Penicillin is an antibiotic substance, existing in several forms, that is derived from certain species of molds belonging to the genus, *Penicillium*, by extraction of cultures grown on special media. The various forms of penicillin, so far isolated, have been designated as F, G, K, and X. Their structural formulas may be represented as follows:



Penicillin preparations have been widely employed in the form of the sodium or potassium salt. The preparations of greater activity are designated as G, K, and X. The sodium or potassium salt have also been developed. Penicillin in any form is required to be certified under the regulations of the Food and Drug Administration.

Penicillin mixtures for parenteral or oral use are limited by the Food and Drug Administration to a content of not more than

to 100 C for four hours. The material is required to have a potency of not less than 60 units per gram or when coarsely powdered, a potency of not less than 60 units per gram.

The material is required to contain not less than 60 units of penicillin per gram of the Food and Drug Administration master standard and is approximately equivalent to the original Oxford unit. Potency is assayed by bacteriologic testing against a strain of *Staphylococcus aureus* or other suitable organisms.

60 or above retain their potency for a minimum of seven days. Tablets should be protected against moisture to prevent deterioration.

Troches

Action and Uses.—Penicillin in either the crystalline or amorphous form is chiefly effective against gram positive bacteria, particularly against staphylococcal, streptococcal, pneumococcal, and clostridial infections, but also against gram negative gonococcal and meningococcal infections. It is also effective in bacterial endocarditis due to susceptible organisms and against anthrax infection. It has been found useful in the treatment of syphilis, leptospirosis, Vincent's infection, actinomycosis and infection with *Streptobacillus moniliformis*, but its ultimate curative value in these conditions is not yet clearly defined. It is contraindicated in patients with a history of allergic reactions to penicillin.

comitant use of adequate amounts of antitoxin and of at least 240 000 units of penicillin per day for a period of not less than 10 days.

infections nonspecific inflammatory conditions tuberculosis amebiasis malaria and neoplastic diseases.

Penicillin is essentially nontoxic though delayed urticarial reactions have occurred with its systemic use. Applied locally it

may produce epidermal sensitivity in as many as 10 per cent of cases, particularly in patients with pyoderma.

CAUTION

PENICILLIN FOR PARENTERAL USE IN AQUEOUS SOLUTION

Penicillin in the form of *penicillin G*

sodium salt
: solution of
n concentra-
ions may be

made subcutaneously, intramuscularly or intravenously. Latter route is used only for continuous infusion of concentration of from 25 to 50 units per cubic centimeter at the rate of from 5,000 to 10,000 units per hour. Owing to the rapid excretion of the aqueous solutions of penicillin, injections must be repeated every three or four hours in order to maintain therapeutic blood levels.

In severe infections continuous intravenous infusion of a solution containing from 25 to 50 units per cc. should be administered at a uniform rate of from 5,000 to 10,000 units per hour. Concentrations of 25,000 to 50,000 units per cc. may be used for intrathecal

because p
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arachnoid space should be restricted to the concentration and amounts indicated above.

Dosage—In serious penicillin-susceptible infections, with or without bacteremia, the average dosage is from 300,000 to 600,000 units per 24-hour period; in chronic pyogenic infections, as an adjunct to surgical treatment, the dosage should be from 50,000 to 100,000 units every six hours; in acute gonorrhea, doses of 25,000 units every three hours may be given to hospitalized patients.

In meningitis, endocarditis and infections complicated by abscess formation or involving serous cavities parenteral administration is the preferred form of therapy and should be the acute con- other modes of

In the prophylaxis of subacute bacterial endocarditis a minimum of 600,000 units daily should be employed.

In seronegative primary syphilis, 60,000 units should be given intramuscularly every 3 or 4 hours for a total of at least 3,600,000 units; for seropositive primary and early secondary syphilis, a total of 90 similar doses are given for a total of 5,400,000 units.

Large single doses of 250,000 units or more of aqueous crystal-

line penicillin administered intramuscularly once every 12 hours are considered adequate in uncomplicated pneumococcus pneumonia but the shorter dosage interval is preferred when less susceptible infections are treated

ABBOTT LABORATORIES

Sodium Penicillin 100 000 200 000 500 000 and 1 000 000 unit vials

Crystalline Potassium Penicillin G 100 000 200 000 500 000 1 000 000 and 5 000 000 unit vials

BIO-RAMO DRUG CO

Sodium Penicillin 200 000 and 500 000 unit vials

Crystalline Sodium Penicillin G 200 000 500 000 and 1 000 000 unit vials Buffered with sodium citrate

BRISTOL LABORATORIES INC

Calcium Penicillin 100 000 and 200 000 units 20 cc. vials

Sodium Penicillin 100 000 units 20 cc vials

Crystalline Sodium Penicillin 100 000 200 000 and 500 000 units 20 cc vials and in combination packages containing a vial of sodium penicillin and a 2 cc. vial of isotonic salt solution

BURROUGHS WELLCOME & CO INC

Sodium Penicillin 100 000 unit bottles

COMMERCIAL SOLVENTS CORPORATION

Calcium Penicillin 100 000 unit vials

Sodium Penicillin 100 000 unit vials

Crystalline Potassium Penicillin G 100 000 200 000 and 500 000 units 20 cc vials and 1 000 000 units 50 cc vials

Crystalline Sodium Penicillin G 100 000, 200 000 and 500 000 units 20 cc vials and 1 000 000 units 50 cc vials

R. L. DWIGHT & COMPANY

Crystalline Potassium Penicillin G 100 000 200 000 500 000 and 1 000 000 unit vials.

HEYDEN CHEMICAL CORPORATION

Calcium Penicillin 100 000 and 200 000 unit ampuls and vials

Sodium Penicillin 100 000 200 000, 500 000 and 1 000 000 units 2 cc vials

LEDFRE LABORATORIES DIVISION AMERICAN CYANAMID CO.

Sodium Penicillin 100 000 unit vials

Crystalline Sodium Penicillin G (Buffered) 100 000 200 000 and 500 000 unit vials Buffered with sodium citrate
U S P

ELI LILLY & Co.

Sodium Penicillin: 100,000 and 200,000 unit ampuls.

Crystalline Potassium Penicillin G: 100,000, 200,000, 500,000 and 1,000,000 units, 20 cc. vials.

Crystalline Sodium Penicillin G: 100,000, 200,000, 500,000 and 1,000,000 units, 20 cc. vials

MERCK & Co, INC.

Calcium Penicillin: 100,000 and 200,000 unit vials.

Sodium Penicillin: 100,000 and 200,000 unit vials.

Crystalline Sodium Penicillin G: 100,000, 200,000 and 500,000 units, 20 cc. vials.

THE WM. S. MERRELL CO.

Sodium Penicillin: 100,000, 200,000, 500,000 and 1,000,000 unit vials.

PARKE, DAVIS & COMPANY

Sodium Penicillin: 100,000 unit vials.

CHAS. PFIZER & Co.

Calcium Penicillin: Bulk, 1,000,000,000 unit bottles.

Sodium Penicillin: 100,000 unit bottles.

Crystalline Potassium Penicillin G: 100,000, 200,000 and 500,000 unit bottles. Bulk, 1,000,000,000 unit bottles.

Crystalline Sodium Penicillin G: 100,000, 200,000, 500,000 and 1,000,000 unit vials. Bulk, 1,000,000,000 unit bottles.

PREMO PHARMACEUTICAL LABORATORIES, INC.

Crystalline Sodium Penicillin G: 100,000, 200,000, 500,000 and 1,000,000 units, 20 cc. vials.

SCHENLEY LABORATORIES, INC.

Calcium Penicillin: 200,000 units, 20 cc. vials.

Sodium Penicillin: 100,000, 200,000 and 500,000 units, 20 cc. vials and 1,000,000 units, 10-cc. vials

Crystalline Potassium Penicillin G: 100,000, 200,000, 500,000 units, 20 cc. vials; 1,000,000 units, 50 cc vials.

E. R. SQUIBB & SONS

Crystalline Sodium Penicillin G: 500,000 and 1,000,000 unit vials.

Crystalline Sodium Penicillin G (Buffered), 100,000 and 200,000 unit vials. Buffered with sodium citrate.

TAYLOR UNION COMPANY

Crystalline Sodium Penicillin G 100,000, 200,000, 500,000 units per cc., 25 cc. vials; 1,000,000 units per cc., 50 cc. vials; and 100,000 units in single combination packages with 20 cc. vials of sterile isotonic sodium chloride solution.

WILLIAM F. WARRER & Co., Inc.

Sodium Penicillin 100,000 unit ampuls.

WINTHROP STEARNS, INC.

Sodium Penicillin 100,000 and 200,000 unit vials.

WYETH INCORPORATED

Calcium Penicillin 100,000 unit vials.

Sodium Penicillin 200,000 and 500,000 unit vials.

PENICILLIN FOR PARENTERAL USE FOR PROLONGED ACTION

The blood levels of penicillin may be prolonged beyond the 3 to 4 or 6 hour period by various means. Vehicles which delay absorption, such as a mixture of a vegetable oil and beeswax (Kernansky formula) allow the penicillin to be slowly absorbed from an intramuscular "depot." Insoluble salts such as the procaine salt of penicillin act similarly. Excretion may be delayed by the simultaneous administration of renal blocking agents such as para-aminosalicylic acid or carotennamide.

The absorption of penicillin from "free flowing" mixtures of oil and wax is influenced by the particle size of the penicillin crystals; if the particles are less than 50 microns in diameter absorption is hastened. The regulations of The Food and Drug Administration provide that 50 per cent or more of the penicillin particles in a mixture shall be 50 microns or greater in diameter. On the other hand, the presence of small particles in preparations of procaine penicillin G in oil with 2 per cent aluminum monostearate appears to enhance the prolongation of penicillin action.

Penicillin in oil and wax exerts a prolonged effect and may achieve adequate blood levels in concentrations of 30,000 units per cubic centimeter (equivalent to 100,000 to 125,000 U.P.U. per cc.) or even as low as 10,000 units per cubic centimeter. The following table shows the blood levels of penicillin in oil and wax preparations. The concentration of penicillin in the oil and wax is 100,000 units per cc. The blood levels of penicillin in the oil and wax preparations are shown in the following table. The blood levels of penicillin in the oil and wax preparations are shown in the following table. The blood levels of penicillin in the oil and wax preparations are shown in the following table.

levels 4 hours after injection are usually lower than those following injection of the oil and wax preparations. Procaine penicillin G is no more toxic than other penicillin preparations, and intramuscular injection is reported to be virtually painless.

Dosage.—Penicillin in oil and wax and procaine penicillin G in oil may be used in all conditions for which aqueous penicillin solutions are suitable, and are particularly adaptable to the treatment of ambulatory patients or patients who are treated in their homes. A single dose of 300,000 units once every 24 hours will usually suffice for ordinary infections due to penicillin-susceptible organisms. Severe or fulminating infections, including bacterial endocarditis, should be treated with doses of 600,000 units given once or twice daily.

ABBOTT LABORATORIES

Calcium Penicillin in Oil and Wax: 300,000 units per cc., in peanut oil containing 4.8 per cent (W/V) white wax, U. S. P., in B-D¹ 1 cc. glass cartridge with B-D Disposable Cartridge Syringe; and in B-D 1 cc. cartridge, with flushing fluid (benzyl alcohol 1.5 per cent in isotonic solution of sodium chloride), for use in B-D Cartridge Syringe.

Crystalline Procaine Penicillin G in Oil: 300,000 units per cc. in sesame oil with 2 per cent aluminum monostearate, 1 cc. cartridges with B-D disposable syringes; 300,000 units per cc. in sesame oil, 10 cc. vials.

¹ Trademark registered, Becton, Dickinson & Co

BIO-RAMO DRUG COMPANY

Calcium Penicillin in Oil and Wax: 300,000 units per cc., 10 cc. vials.

BRISTOL LABORATORIES, INC.

Calcium Penicillin in Oil and Wax: 300,000 units per cc., in peanut oil containing 4.8 per cent (W/V) white wax, U. S. P., 10 cc. vials.

Crystalline Sodium Penicillin G in Oil and Wax (Free Flowing): 300,000 units per cc. in peanut oil containing 4.8 per cent (W/V) white wax U. S. P. 1 cc. cartridges and 10 cc. vials.

GREENHILL CORPORATION

Calcium Penicillin in Oil and Wax: 300,000 units per cc. (W/V) white wax, in package with disposable; five 1 cc. glass cartridges and syringe assembly consisting of metal syringe and two stainless steel 1½ inch (3.8 cm.) 20 gauge needles.

Crystalline Potassium Penicillin G in Oil and Wax: 300,000 units per cc., in peanut oil containing 4.8 per cent (W/V) white wax, U. S. P., 10 cc. and 20 cc. vials.

Crystalline Potassium Penicillin G in Oil and Wax (Free Flowing) • 300 000 units per cc 10 cc vials

Crystalline Procaine Penicillin G (Micronized) in Oil, 300 000 units per cc in 2 per cent hydrogenated peanut oil with aluminum monostearate, 10 cc vials

ELI LILLY & Co

Crystalline Potassium Penicillin G in Oil and Wax 300 000 units per cc in peanut oil containing 4.8 per cent (W/V) white wax, U S P 1 cc glass cartridges with B D¹ Disposable Cartridge Syringe and 10 cc ampuls

¹ Trademark registered Becton Dickinson & Co

THE WM S MERRILL Co

Crystalline Procaine Penicillin G in Oil 300 000 units per cc in sesame oil 10 cc vials

Crystalline Sodium Penicillin G in Oil and Wax; 300 000 units per cc in peanut oil containing 4.8 per cent (W/V) white wax U S P 10 cc vials

CHAS PFIZER & Co INC

Crystalline Procaine Penicillin G Bulk 100 000 000 units

Crystalline Procaine Penicillin G in Oil 300 000 units per cc in sesame oil 10 cc vials.

PREMO PHARMACEUTICAL LABORATORIES INC

Crystalline Potassium Penicillin G in Oil and Wax 300 000 units per cc in peanut oil containing 4.8 per cent (W/V) white wax U S P, 5 cc and 10 cc vials

Crystalline Procaine Penicillin G (Micronized) in Oil 300 000 units per cc in sesame oil with aluminum monostearate 2 per cent (W/V) 1 cc disposable syringes 1 cc glass syringes and 10 cc vials

Crystalline Sodium Penicillin G in Oil and Wax 300 000 units per cc in sesame oil containing 4.8 per cent (W/V) white wax U S P 1 cc glass disposable syringe and 5 cc vials

E R Squibb & Sons

Crystalline Procaine Penicillin G in Oil 300 000 units per cc in sesame oil, 1 cc and 10 cc vials 300 000 units per cc in peanut oil suspended with 2 per cent aluminum monostearate, 10 cc vials 1 cc double cell cartridge one cell containing 300 000 units procaine penicillin G in peanut oil with 2 per cent aluminum monostearate the other cell containing sterile aspirating test solution with 0.5 per cent chlorobutanol available in packages of five cartridges for use with the metal B D cartridge syringe assembly and in a combination package with the B D Disposable Cartridge Syringe

STERONE CHEMICAL COMPANY, INC.

Calcium Penicillin in Oil and Wax: 300,000 units per cc., in sesame oil containing 48 per cent (W/V) white wax, U. S. P., 1 cc. cartridges and 10 cc. vials.

PENICILLIN FOR ORAL ADMINISTRATION

Penicillin may be administered orally although it is necessary to use large amounts in order to achieve significant blood levels owing to the fact that the drug is partially inactivated by the gastric juice and, in the lower bowel, by certain bacterial enzymes. Furthermore, absorption from the gastro-intestinal tract is irregular, hence oral administration requires doses of approximately five times the amount usually recommended for injection. Oral doses should be given between meals, preferably buffered with a suitable antacid, such as sodium citrate, aluminum dihydroxy amino acetate, or aluminum hydroxide, although this may be unnecessary with crystalline products prepared in a suitable physical state or with tablets of aluminum penicillin. Soluble penicillin salts may also be added to the milk formula of infants.

Dosage—In meningitis, endocarditis and infections complicated by abscess formation or involving serous cavities, penicillin should be administered parenterally; in acute infections with bacteremia or septicemia, parenteral administration should be continued until blood cultures become negative and the acute condition is controlled. Oral penicillin alone, should be relied upon in acute infections only when the patient responds promptly to treatment; uncomplicated gonorrhea, acute streptococcal infections of the respiratory tract, pneumococcal pneumonia, and certain mild staphylococcal infections may be treated successfully with adequate doses of oral penicillin. Against secondary infections after tonsillectomy or tooth extraction in cases with a history of rheumatic fever or rheumatic heart disease, congenital heart disease and other conditions in which secondary infections may occur, oral doses of 300,000 to 600,000 units daily in divided doses should be given from one day before to three or four days after surgery.

ABBOTT LABORATORIES

Tablets Crystalline Potassium Penicillin G (Buffered): 10,000 and 50,000 units Buffered with calcium carbonate 0.25 Gm.

Dulcet Tablets Crystalline Potassium Penicillin G (Buffered): 50,000 units. Buffered with calcium carbonate 0.25 Gm.

U. S. trademark 500,527.

BRISTOL LABORATORIES, INC.

Tablets Calcium Penicillin (Buffered): 50,000 units. Buffered with calcium carbonate 0.5 Gm.

COMMERCIAL SOLVENTS CORPORATION

Tablets Crystalline Potassium Penicillin G 50 000 units
2 cc. vials each containing two tablets for the preparation of
sterile solution

Tablets Crystalline Potassium Penicillin G (Buffered)
100,000 units Buffered with glycerides and sodium salts of fatty acids

Eli Lilly & Co.

Tablets Crystalline Potassium Penicillin G (Buffered)
50 000 and 100 000 units. Buffered with sodium citrate

PREMO PHARMACEUTICAL LABORATORIES, INC.

Tablets Calcium Penicillin (*Buffered*) 50 000 units and 100 000 units. Buffered with calcium carbonate 0.25 Gm

Tablets Crystalline Potassium Penicillin G (Buffered)
50 000 and 100 000 units Buffered with calcium carbonate 0.25 Gm

SCHEFFLE LABORATORIES, INC.

Tablets Calcium Penicillin (*Buffered*) 50 000 units Buf
fered with calcium carbonate 0.45 Gm

L. R. SOLIH & SONS

Tablets Sodium Penicillin G (Buffered) 50 000 and 100 000 units. Buffered with trisodium citrate 0.5 Gm.

THE UNION COMPANY

Tablets Crystalline Potassium Penicillin G (Buffered)
50 000 100 000 and 250 000 units Buffered with calcium tar-
trate 0.25 Gm.

PENICILLIN FOR INHALATION THERAPY

Intracavitary therapy by inhalation through the nebulizing of from 25 000 to 50 000 units per cc. every three to four hours provides good blood levels and is a useful method in the treatment of chronic pulmonary infection. In some instances it has been shown to be an effective adjunct in the treatment of pneumonia. For patients who are not seriously ill and in whom the use of multiple injections are impractical the aerosol treatment can be used for

Soluble tablets are available specially suited for dissolving the drug in a nebulizer for aerosol administration.

Dosage—Is an aerosol from 25 000 to 50 000 units per cc. Should be nebulized and inhaled every three to four hours.

COMMERCIAL SOLVENTS CORPORATION

Soluble Tablets Crystalline Potassium Penicillin G: 50,000 units.

PREMO PHARMACEUTICAL LABORATORIES, INC.

Nebutabs Crystalline Sodium Penicillin G: 50,000 units. For use in the preparation of solutions for nebulization. Packaged with or without an oral nebulizer or with a nasal nebulizer. U. S. patent applied for.

PENICILLIN FOR TOPICAL APPLICATION

Penicillin may be applied topically in powder form, in isotonic sodium chloride solution containing 250 units per cc., or in ointment containing 500 to 5,000 units per gram. The calcium salt is also used in the form of troches for its topical effects against Vincent's stomatitis and other penicillin-susceptible infections of the mouth.

ABBOTT LABORATORIES

Ointment Calcium Penicillin: 1,000 units per gram in white petrolatum, U. S. P., 30 Gm. tubes.

Ophthalmic Ointment Calcium Penicillin: 1,000 units per gram in white petrolatum, U. S. P., 90 per cent and liquid petrolatum, U. S. P., 10 per cent, 4 Gm. tubes.

Troches Crystalline Potassium Penicillin G: 1,000 and 5,000 units.

COMMERCIAL SOLVENTS CORPORATION

Troches Crystalline Potassium Penicillin G: 5,000 units.

ELI LILLY & Co.

Ointment Crystalline Potassium Penicillin G: 1,000 units per gram, 28 Gm. tubes.

Ophthalmic Ointment Crystalline Potassium Penicillin G: 1,000 units per gram, 35 Gm. tubes.

Troches Crystalline Potassium Penicillin G: 5,000 units.

PREMO PHARMACEUTICAL LABORATORIES, INC.

Ointment Calcium Penicillin: 2,000 and 5,000 units per gram, 28.5 Gm. tubes in a base consisting of white petrolatum U. S. P. and anhydrous wool fat

Troches Calcium Penicillin: 5,000 units.

Troches Crystalline Potassium Penicillin G: 5,000 units.

SCHENLEY LABORATORIES, INC.

Ointment Calcium Penicillin: 1,000 units per gram, 28.35 Gm. tubes in white petrolatum, U. S. P., 78 per cent, mineral oil 3.5 per cent, beeswax 35 per cent and anhydrous lanolin, U. S. P., 15 per cent.

Ophthalmic Ointment Calcium Penicillin 2,000 units per gram, 3.54 Gm. tubes in white petrolatum, U S P

Troches Calcium Penicillin 1,000 units

E. R. Squibb & Sons

Ointment Calcium Penicillin 1,000 units per gram, 15 30 and 60 Gm. tubes, in a base consisting of petrolatum 40 per cent, beeswax 4 per cent, anhydrous lanolin 10 per cent and peanut oil approximately 46 per cent.

Ophthalmic Ointment Calcium Penicillin 1,000 units per gram 36 Gm. tubes in a base consisting of petrolatum 40 per cent beeswax 4 per cent, anhydrous lanolin 10 per cent and peanut oil approximately 46 per cent

Chewing Troches Calcium Penicillin 20,000 units

THE UPJOHN COMPANY

Ointment Calcium Penicillin 1,000 units per gram, 28.35 Gm. tubes

Ophthalmic Ointment Calcium Penicillin 1,000 units per gram, 39 Gm. tubes

Troches Crystalline Potassium Penicillin G 5,000 units.

WINTHROP-STEARN'S, INC.

Ophthalmic Ointment Calcium Penicillin 1,000 units per gram 3.54 Gm. tubes in a base consisting of white petrolatum, U S P., 60 per cent and liquid petrolatum, U S P., 20 per cent and lanolin anhydrous U S P., 20 per cent

Streptomycin

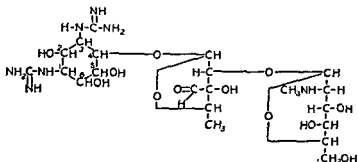
Streptomycin is a purified active antibiotic principle produced by certain strains of *Streptomyces griseus* when they are grown on suitable media. It has the property of inhibiting the growth and of occasionally destroying certain gram positive and gram negative bacteria. It may be prepared as several salts including the hydrochloride and sulfate salts and the calcium chloride complex double salt (streptomycin trihydrochloride calcium chloride)

It is not a pure product but is marketed as a sterile powder in airtight ampules or vials, the activity in terms of milligrams or grams of pure streptomycin base being declared on the label.

Streptomycin in dry form may be stored at room temperature not exceeding 30° C. for periods up to one year however it should be stored in the original unopened container to prevent contamination and deliquescence. Solutions of streptomycin may be stored at room temperature for one week without significant loss of potency. Solutions which have been acidified or alkalinized, i.e. those having a pH lower than 4 or higher than 7 are less stable. Streptomycin solutions should not be autoclaved.

and only freshly prepared solutions should be used parenterally because of the potential danger of contamination. Streptomycin in any form is required to be certified under the regulations of the Food and Drug Administration.

Merck & Co. give the following structural formula for the active ingredient, streptomycin base:



For tests and standards, see regulation under Sec. 507, Food, Drug and Cosmetic Act, copies of which are obtainable from the Division of Penicillin Control and Immunology Food and Drug Administration, Washington, D. C.

Actions and Uses.—Streptomycin is active in vitro against a wide variety of gram-negative organisms including such pathogens as *Escherichia coli*, *Pasteurella tularensis*, *Hemophilus influenza*, *Pseudomonas aeruginosa*, *Bacillus proteus*, *Eberthella typhosus* and *Brucella abortus*. With certain outstanding exceptions, the in vivo activity of streptomycin parallels its in vitro activity. It also effectively inhibits the growth of a variety of gram-positive organisms such as *Streptococcus hemolyticus*, *Staphylococcus aureus*, *Staphylococcus Bacillus anthracis* and *Corynebacterium*. In many cases of infection due to penicillin-resistant strains.

Streptomycin is not appreciably absorbed when given by the oral route, although it is not significantly destroyed in the gastro-intestinal tract. For systemic action it must be given by the parenteral route. Inhalation of nebulized solutions, intraperitoneal and intrapleural injection are adjunctive modes for administration of streptomycin.

Streptomycin is useful in the treatment of urinary tract infections due to streptomycin-sensitive gram-negative organisms. Streptomycin is of only temporary correction of the *tularensis* is highly susceptible to streptomycin. The most effective treatment for tularemia at present available. Influenzal meningitis due to various *Hemophilus* organisms has been successfully

treated with streptomycin as have Hemophilus infections in other parts of the body. Wound infections, bacteremias, sulfonamide resistant bacillary dysentery, and other infections due to streptomycin susceptible organisms may be treated with this agent.

Experience with streptomycin in the treatment of undulant fever, bacillary dysentery and typhoid has been disappointing and failure of therapy has been the rule. Until further work elucidates the place of streptomycin in these infections its use cannot be recommended.

Although streptomycin shows promising results in the therapy of tuberculous infections in guinea pigs, the clinical experience in human infections has not been sufficiently large to delineate its precise role in the control of all forms of human tuberculosis. Striking results have been obtained in certain patients with miliary and tuberculous meningitis. In these cases streptomycin is mandatory. Excellent results have been obtained in patients with tuberculous sinuses—and in patients with mucous membrane and laryngeal tuberculosis. The results have also been impressive in tuberculous enteritis and peritonitis. In renal tuberculosis the dysuria and frequency are often reduced and the capacity of the bladder increased. The pyuria decreases, the number of organisms decrease although complete cure of the process is infrequent. In pulmonary tuberculosis at least 50 to 80 per cent of patients with predominately exudative lesions show improvement.

Streptomycin is capable of producing side reactions of varying severity. The most serious toxic effect is its neurotoxic action on the eighth nerve which may occur in about 10 per cent of patients treated with large doses (3 to 4 Gm. daily) over periods of several weeks to months. This is characterized by vertigo, tinnitus, disturbance of equilibrium and diminished auditory acuity. On cessation of therapy, partial recovery of eighth nerve function is the rule although this recovery is slow and vestibular function appears to be permanently impaired although compensation occurs. Minor toxic effects include skin rashes, mild malaise, muscular aching and drug fever.

Streptomycin has been found to possess clinical effectiveness in the treatment of three forms of venereal disease: granuloma inguinale, chancroid and gonorrhea. It is the drug of choice in the treatment of granuloma inguinale and it may be used alone or in conjunction with antimony compounds. Although effective in chancroid, the sulfonamides provide a convenient and equally effective treatment and streptomycin need only be used for the rare patient infected with sulfonamide resistant *Ducrey bacilli* or for patients sensitive to sulfonamide preparations. In the treatment of gonorrhea there is little choice between penicillin and streptomycin. Until further experience provides information on the effect of streptomycin on *T. pallidum* it is wise to pursue the same course in following the blood serology in patients treated for gonorrhea with streptomycin as is pursued following treatment with penicillin.

Dosage.—For intramuscular injection, the powder should be dissolved in sterile, pyrogen-free distilled water or isotonic solution of sodium chloride to give a concentration of from 100 to 200 mg. of streptomycin base per cubic centimeter. For subcutaneous injection, more dilute solutions are recommended. If the drug is administered by intravenous drip, 1 to 2 Gm. dissolved in a liter of isotonic solution of sodium chloride may be administered at a rate of about 25 drops per minute. For er cubic centimeter be used. For topical mg. per cubic centimeter may be used.

The dosage of streptomycin should be governed by the susceptibility of the organism responsible for the infection. In doses of 2 to 4 Gm. daily may be

. doses of the intra- two days dministra-
tion of streptomycin.

It is important to give sufficiently large doses to inhibit or kill the infecting organisms quickly, since the development of "fastness" to streptomycin is common and may occur rapidly. Inadequate dosage predisposes to the development of resistant strains of the organisms.

ABBOTT LABORATORIES

Streptomycin Sulfate: 20 cc. vials containing streptomycin sulfate equivalent in activity to 1 Gm. of streptomycin base (one million units)

MERCK & Co., INC

Streptomycin Calcium Chloride Complex: 20 cc. or 50 cc. vials containing streptomycin calcium chloride complex equivalent in activity to 1 Gm. or 5 Gm. of streptomycin base, respectively.

THE WM. S. MERRELL CO

Streptomycin Calcium Chloride Complex: 20 cc. or 50 cc. vials containing 1.3 Gm. or 6.5 Gm. of streptomycin calcium chloride complex equivalent to a 1.0 Gm. or 5.0 Gm. of streptomycin base, respectively.

CHAS PRIZER & Co., Inc.

Streptomycin Sulfate Bulk.

Streptomycin Sulfate 20 cc. vials containing streptomycin sulfate equivalent in activity to 1 Gm. of streptomycin base

FREMO PHARMACY —

Streptomycin (.) 20 cc. vials containing streptomycin sulfate equivalent to 1 Gm. of streptomycin base

Streptomycin Sulfate 20 cc. vials containing streptomycin sulfate equivalent in activity to 1 Gm. of streptomycin base

L. R. SQUIBB & SONS

Streptomycin Hydrochloride 20 cc. or 40 cc. vials equivalent in activity to 1 Gm. or 2 Gm. of streptomycin base, respectively

THE UPJOHN COMPANY

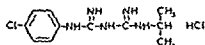
Streptomycin Sulfate 30 cc. vials containing streptomycin sulfate equivalent in activity to 1 Gm. of streptomycin base (one million units)

TYROTHRICIN — (See under Local Anti Infectives)

ANTIMALARIAL AGENTS

Synthetic Compounds

CHLORGUANIDE HYDROCHLORIDE — Guanatol Hydrochloride (LILLY) — N^1 (*p*-chlorophenyl)- N^2 -isopropylbiguanide hydrochloride — The structural formula of chlorguanide hydrochloride may be represented as follows



For tests and standards see Section B

Actions and Uses — Chlorguanide hydrochloride is a powerful prophylactic agent in the treatment of *Plasmodium vivax* malaria. It is also partly effective in preventing attacks of vivax malaria since erythrocytic forms appear in the blood a short time after the drug is withdrawn. Other antimalarial drugs such as chloroquine or quinacrine are said to be preferred in the treatment of vivax malaria. Chlorguanide hydrochloride is the drug of choice for the treatment of falciparum malaria.

Chlorguanide hydrochloride disappears from the plasma in about 48 hours after the administration of a single dose of 0.5 Gm. About one-half to one-third of the drug is excreted by the kidneys. The drug does not accumulate in the body when given in therapeutic doses.

No toxic symptoms are observed in the usual dosage regimen, but doses of 10 Gm. or more may produce vomiting, abdominal pain, and diarrhea. Excessive doses may produce transient hematuria. Intramuscular injection may result in local myositis. High doses may also produce a temporary myelocytic reaction in the blood.

As with other antimalarial agents, the response of various strains of plasmodia to the drug is variable, so that the average dosage schedule indicated below may be subject to modification in accordance with the response of the strain involved.

Dosage—A single dose of 0.3 Gm. weekly in the suppression of falciparum and vivax malaria. For the prophylaxis of falciparum malaria, 0.1 Gm. twice weekly may be given; this dose is only partially effective against vivax malaria.

A dose of 0.1 Gm. three times daily, or 0.3 Gm. daily, for ten days is usually effective in producing a cure of falciparum malaria. The same dose is usually only partially effective against vivax malaria.

ABBOTT LABORATORIES

Tablets Chlorguanide Hydrochloride: 0.1 Gm. and 0.3 Gm.

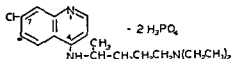
ELI LILLY & Co

Tablets Guanatol Hydrochloride: 25 mg., 50 mg. and 100 mg.

SYNTAM LABORATORIES, INC

Tablets Chlorguanide Hydrochloride: 0.1 Gm.

CHLOROQUINE DI-POSSPHATE (Chloroquine diphosphate) (methylbutylphosphate) formula of chloroquine diphosphate may be represented as follows.



For tests and standards, see Section B.

Actions and Uses.—Chloroquine diphosphate is highly active against the erythrocytic forms of *P. vivax* and *P. falciparum*. It does not prevent relapses in vivax malaria, nor will it pre-

In falciparum malaria, chloroquine diphosphate abolishes the acute attack and effects complete cure of the infection.

Chloroquine diphosphate has approximately three times the activity of quinacrine hydrochloride against standardized strains of *P. vivax* and *P. falciparum*.

Chloroquine diphosphate is rapidly and completely absorbed by the gastro-intestinal tract. Some of it is excreted slowly in the urine. Considerable amounts are deposited in the organs and tissues and it is concentrated in nucleated cells, particularly those of the liver, spleen, kidneys and lung.

Chloroquine diphosphate is metabolized in the body, but this occurs slowly and the drug may be detected in body tissues for more than a week after discontinuing medication. The drug is well tolerated in therapeutic doses and does not produce cinchonism nor discolor the skin. However, there may be mild headache, pruritis, visual disturbances and gastro-intestinal complaints following therapeutic doses. Blurring of vision and difficulty in focusing are occasionally observed following prolonged administration. None of the side reactions appear serious and all have been of a reversible nature.

Dosage—Chloroquine diphosphate is usually administered orally either before or after meals. For suppression of vivax malaria, a weekly dose of 0.5 Gm. given at exactly seven-day intervals is recommended.

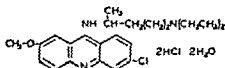
For treatment of acute attacks of vivax and falciparum malaria an initial dose of 1.0 Gm. followed by an additional 0.5 Gm. after six to eight hours and a single dose of 0.5 Gm. on each of two consecutive days (total of 2.5 Gm. in three days) is sufficient to eradicate most infections with *P. falciparum* and to terminate an acute attack of vivax malaria. In the latter, freedom from clinical attacks may be maintained thereafter by administration of suppressive doses (0.5 Gm. weekly).

WINTHROP-STEARNS INC.

Tablets Aralen Diphosphate 0.25 Gm.

U. S. patent 2,233,970 (March 4 1941 expires 1958) U. S. trademark registered pending

QUINACRINE HYDROCHLORIDE—U. S. P.—Atabrine dihydrochloride (WINTHROP-STEARNS)—3-Chloro-7-methoxy-9-(1-methyl-4-diethylaminobutylamino)acridine dihydrochloride dihydrate—Mepacrine Hydrochloride—Contains not less than 77 per cent and not more than 80.2 per cent of quinacrine base $C_{21}H_{20}ClN_3O$ corresponding to not less than 98 per cent of $C_{21}H_{20}ClN_3O \cdot 2HCl \cdot 2H_2O$ —U. S. P. The structural formula may be represented as follows:



For description and standards see the U. S. Pharmacopeia

under Quinacrine Hydrochloride and Quinacrine Hydrochloride Tablets.

Actions and Uses.—Quinacrine hydrochloride destroys the asexual forms (trophozoites) of the causative organism in all types of malaria and thus checks the progress of the disease. Given during the first paroxysms of a benign tertian (*P. vivax*) attack it will often prevent completely the appearance of the third paroxysm while considerably lessening the severity of the second. At present the consensus is that in ordinary cases of benign type, and also in the more rare quartan (*P. malariae*) type, it gives better results than quinine. Some observers are of the opinion that relapses are less frequent than with quinine and that the period of treatment is shorter. Quinacrine hydrochloride is more effective than quinine in the treatment of malignant subtertian (*P. falciparum*) malaria. It is of value in the treatment of blackwater fever when the treatment of quinine is contraindicated. Like quinine the drug effects partial destruction

Quinacrine hydrochloride is reported to be effective in combating *Giardia lamblia* infestation, but the evidence that this organism is pathogenic for man or is the cause of diarrhea and other symptoms associated with its presence in the gastro-intestinal tract is inconclusive.

Quinacrine hydrochloride causes the urine to become very yellow on the third to fifth day, and, being of an acridine dye nature, it may cause temporary discoloration of the skin. Headache and relatively mild gastro-intestinal symptoms occur but not very frequently. The drug does not cause visual or aural disturbances and may therefore be preferred to quinine by patients who have experienced both drugs. The circulatory system does not seem to be disturbed by quinacrine hydrochloride in therapeutic dosage. The drug is not considered to be toxic to the
 of psychotic at-
 quite severe—but
 i Apparently the
 pregnancy though

many observers withhold it in toxemia.

Quinacrine hydrochloride is absorbed readily from the intestine and is excreted slowly in the urine and feces. It is usually given by mouth but may also be given intravenously or intramuscularly, the latter route being preferred if injection must be resorted to at all.

Dosage.—

Therapeutic Dose for clinical malaria. Adults: 2 tablets of 0.1 Gm. each and sodium bicarbonate 1 Gm. by mouth with

200 to 300 cc of water (or an equal amount of sweetened tea or fruit juice) every six hours for 5 doses, then 1 tablet of 0.1 Gm. 3 times daily for 6 days

Children, 1 to 4 years 1 tablet of 0.1 Gm. 3 times daily for the first day, then 1 tablet of 0.1 Gm. once daily for 6 days

Children, 4 to 8 years 2 tablets of 0.1 Gm. 3 times daily for the first day, then 1 tablet of 0.1 Gm. twice daily for 6 days

Over 8 years Same as adults

Suppressive Dose in malarious areas Adults 1 tablet of 0.1 Gm. daily, preferably beginning two weeks in advance of exposure, and continuing for at least four weeks after last possible exposure in a malarious area

Children 1 tablet of 50 mg. daily

Suppressive Dose in persons who have had attacks of vivax malaria within 6 months and no quinacrine (atabrine) for 3 weeks

Adults 1 tablet of 0.1 Gm. 3 times a day for 3 days, then 1 tablet of 0.1 Gm. daily

Children 1 tablet of 50 mg. 3 times a day for 3 days, then 1 tablet of 50 mg. daily

Note Each dose, therapeutic or suppressive, should be taken with a full glass of water after a meal

The technic of the intramuscular or intravenous administration must be learned before the method is used. Details will be found in the circulars of manufacturers and in various publications

WINTHROP STEARNS, INC.

Atabrine di-Hydrochloride (Powder) 0.2 Gm. ampuls packaged with 10 cc. ampuls of sterile distilled water

Tablets Atabrine di-Hydrochloride 50 mg. and 0.1 Gm. (plain) and 0.1 Gm. (sugar coated)

U. S. patent 2,113,357 (April 3, 1938, expires 1955) U. S. trade mark 302,473

Naturally Occurring Compounds

The action of quinine is essentially the same in all its com-

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cause of the danger of local tissue damage. In those rare cases where neither or the use of other

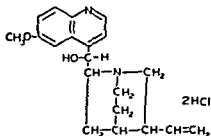
Some of the radicals (pheneti

their characteristic effects; but it is doubtful whether the combinations of several therapeutically active radicals in fixed proportions are superior to simple mixtures of the ingredients.

Totaquine, U. S. P., which is a mixture of alkaloids from the bark of species of *Cinchona* containing not less than 70 per cent of the total crystallizable alkaloids has been developed for use in the treatment of malaria in the same manner as quinine compounds.

QUININE DIHYDROCHLORIDE-U. S. P.—"The dihydrochloride of an alkaloid obtained from cinchona." *U. S. P.*

For description and standards see the U. S. Pharmacopeia under Quinine Dihydrochloride and The National Formulary under Quinine Hydrochloride Ampuls. The structural formula may be represented as follows:



Actions and Uses.—Quinine Dihydrochloride has actions similar to those of quinine, over which it has the advantage of being more soluble in water. It is used where aqueous solutions of quinine are desired for intravenous injection in those cases of severe malarial infection where oral medication is not feasible. It should not be administered by subcutaneous or intramuscular injection because of the danger of local tissue damage. The

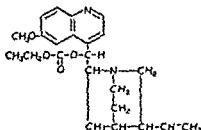
lar impairment.

Dosage.—From 0.24 to 0.65 Gm, suitably diluted, is given intravenously as indicated by the severity of the symptoms and the age of the patient. The dose of 0.65 Gm. should not be repeated more than three times in twenty-four hours. Oral administration should be resumed as early as possible.

ENDO PRODUCTS, INC.

Solution Quinine Dihydrochloride: 0.25 Gm, 1 cc.; 0.5 Gm., 1 cc.; 1.0 Gm., 2 cc. ampuls. Each ampul contains the stated amount of quinine dihydrochloride dissolved in distilled water.

as follows:



For description and standards see The National Formulary under Quinine Ethylcarbonate

Actions and Uses—Quinine ethylcarbonate is used in place of quinine sulfate and similar soluble quinine salts when a practically tasteless quinine compound is preferred.

Dosage—1 Gm.

MALLINCKRODT CHEMICAL WORKS

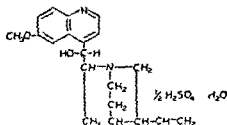
Quinine Ethyl Carbonate (Powder): Bulk.

MEYER & Co, Inc.

Euquinine (Quinine Ethylcarbonate Crystals). Bulk

QUININE SULFATE—U. S. P.—Coco-Quinine (Lilly)

—“The sulfate of an alkaloid obtained from cinchona.” U. S. P.
The structural formula may be represented as follows:



For description and standards see the U. S. Pharmacopeia under Quinine Sulfate and The National Formulary under Quinine Sulfate Capsules

Actions and Uses—Quinine is a protoplasm poison, affecting protozoa more than bacteria. It is somewhat irritating to the stomach and intestines and when absorbed it may cause ringing in the ears, but moderate doses usually produce no other marked effects in healthy persons though hypersensitivity to quinine

is not rare. In patients with fever it is antipyretic. It is used

doses of quinine act as a stimulant to the uterine muscles, but do not produce such spasmodic contractions as ergot. Quinine may be used as a tonic, as are the simple bitters, for the improvement of digestion and nutrition. It has recently come into use for the treatment of myotonia, for which large doses may be required. Its solutions, and especially those of quinine and urea hydrochloride, produce local anesthesia. The ordinary quinine salts are irritant.

Dosage.—1 Gm. daily. For ordinary use it is preferably administered in the form of capsules. For use as a bitter tonic 0.1 Gm. is given in solution.

ELI LILLY AND COMPANY

Syrup Coco-Quinine: Each 100 cc. contains quinine sulfate, 2.19 Gm. suspended in a syrup flavored with chocolate, yerba santa and vanillin, and containing sodium benzoate 0.18 Gm. per 100 cc., and alcohol per cent

U. S. trademark 174,144.

ANTIPROTOZOAN AGENTS

Antimony Compounds

ANTIMONY THIOLYCOLLAMIDE. The thi-
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only
sodium thioglycollate are used in the treatment of schistosomiasis, leishmaniasis (kala-azar), and are proposed for use in the treatment of granuloma inguinale. These substances have been found to be less toxic and less irritating than antimony and

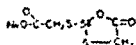
fixed alkalis

HYNSON, WESTCOTT & DUNNING, INC

Antimony Thioglycollamide (Powder): Bulk.

Solution Antimony Thioglycollamide 0.4%: 10 cc. ampuls.

ARTIMONYCOLLATE THIOGLYCOLLATE. The
thioartimonate is formed by dissolving artimony
in a solution of a mixture of sodium thio glycollate and
sodium carbonate. The structural formula may be represented as
follows:



For description and standards see The U.S. Pharmacopeia
and are among such as Triethylamine and Ammonium Sodium
Hydroxide.

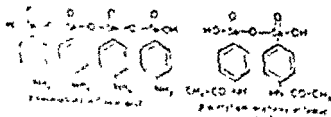
Anterior fat. The same as the anterior thymoglandular. It is more white than anterior thymoglandular, and so I guess it appears to be less toxic.

It is soluble from 0° to 61° C. dissolved in 10 to 20 cc of
cold water, easily 100 cc of boiling water until from 15 to 25
m. There have been given. Its properties are incompatible with
many of the other salts.

[illegible]

Are many Col. am. Thiosulfate (Powder): Bulk

2 ml of Aramyl Sol am Thioglycollate 0.5%: 10 cc.

[illegible]

Actions and Uses.—The pharmacologic effects of antimony preparations depend to some extent on the rapidity with which like antimony is freed from the complex compound. Like all organic antimony compounds, Neostibosan, particularly if injected rapidly into the circulation, may produce a transient fall in systemic blood pressure, due partly to a diminished output of the left ventricle and partly to dilatation of the splanchnic vessels. At the same time, there is a rise in pulmonary blood pressure. Large doses have a depressing effect upon respiration.

After intravenous administration of an average adult dose, it has been found that 41 per cent of the drug is found in the urine during the first twenty-four hours, 6 per cent during the subsequent twenty-four hours, and approximately 1 per cent during the third twenty-four hour period. Following intramuscular administration of the same dose, the figures were 34 per cent, 3 per cent and 1.5 per cent, respectively. The remainder is excreted slowly. Immediate distribution of antimony following a single injection of Neostibosan seems to be dependent on physical factors; no one organ appears to possess immediate affinity. However, following a series of injections, considerable quantities of antimony, which is excreted through the kidneys, may be found in the kidneys and liver.

Included in the reactions that may be encountered are fever, cough, vomiting, nausea, headache, lymphadenitis, skin eruptions, diarrhea, pain in the abdomen, convulsions, nephritis, jaundice, bronchopneumonia and necrosis of the gums. The drug is contraindicated in the presence of nephritis, pulmonary tuberculosis, pneumonia, heart disease, jaundice, diarrhea and ascites.

Ethylstibamine is used in the treatment of certain forms of leishmaniasis (kala-azar, dermal leishmaniasis) but the exact manner by which antimony compounds bring about a cure is unknown; it does not seem to be the result of a direct action on the parasites. Like other pentavalent organic antimony preparations, it is considered less toxic and more effective against kala-azar than trivalent organic antimony compounds.

Dosage.—From 8 to 10 injections are administered daily or every other day. It may be injected intravenously or intramuscularly. A 5 per cent solution is usually employed for intravenous use and a 25 per cent solution (isotonic) for intramuscular injection. *It must be administered slowly.* Solutions should be used immediately and must not be heated. Diet during treatment should be light and easily digestible; the patient should rest for several hours after each injection.

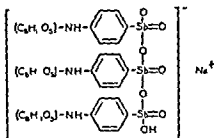
The initial dose for infants is 0.05 Gm.; subsequent doses are increased to 0.1 Gm. For children 2 to 4 years, the initial dose is 0.05 to 0.1 Gm., subsequent doses increased to 0.2 Gm.; 5 to 9 years, initial dose is 0.1 Gm. to 0.2 Gm., subsequent doses increased to 0.25 Gm.; 10 to 15 years, 0.2 Gm. for the initial dose, subsequent doses being increased to 0.3 Gm. Adults may receive 0.2 Gm. as the initial dose, and up to 0.3 Gm. for subsequent doses.

WINTHROP STEARNS, INC.

Neostibosan 0.3 Gm. ampuls

U S patent 1 933 632 U S trademark 400 894

STIBAMINE GLUCOSIDE—A nitrogen glucoside of sodium *p*-aminophenylstibonate—A product of incompletely defined structure prepared by the condensation of *p*-aminophenylstibonic acid and glucose in a slightly basic solution followed by precipitation with absolute alcohol and final drying. The rational formula provisionally assigned to stibamine glucoside is based upon the assumption of a trimer linked through the stibonic group $C_{36}H_{42}O_{22}N_3Sb_3Na$. Stibamine glucoside may be represented by the following structural formula



For tests and standards see Section B

Actions and Uses—Stibamine glucoside shares the antiprotozoan action of other pentavalent organic antimony compounds. In general these are somewhat less toxic than trivalent organic antimony compounds and are considered more effective in the treatment of most forms of leishmaniasis (kala azar) but are of little value in South American leishmaniasis (mucocutaneous) and against the helminths of schistosomiasis (bilharziasis) and filariasis. Trivalent antimony is also usually preferred for the treatment of granuloma inguinale. Antimony compounds have been largely replaced by other drugs in the treatment of these conditions.

Administration—Stibamine glucoside is administered intramuscularly. Reactions include vomiting (about 20 minutes after injection) and occasionally diarrhea. Anaphylactoid reaction characterized by an urticarial eruption, husky voice and in severe cases collapse may be encountered after the sixth or seventh injection. Hepatitis is a rare but serious reaction that calls for immediate cessation of medication.

It is contraindicated in the presence of pneumonia, nephritis, jaundice or ascites.

Dosage—Stibamine glucoside administered intravenously but may be given intramuscularly when superficial veins are not

accessible. The suggested average dose is calculated on the basis of 0.1 Gm. per 100 lb. (45.4 Kg.) of body weight, administered as a freshly prepared 4 per cent solution (0.1 Gm. in 2.5 cc. of sterile distilled water). It is rarely necessary to exceed a maximum single dose of 0.2 Gm. Injections are usually given on alternate days for a course of treatment not to exceed a total dosage of 3 Gm. per 100 lbs. of body weight. This is usually

been given. This more intensive course requires strict observation for the appearance of toxic symptoms. In antimony-susceptible individuals or in whom anaphylactoid reaction is considered likely because of a
advisable to emply
body weight, and
when tolerance is established.

Only solutions prepared from freshly opened containers should be used. The solution should not be warmed for injection and should not be used after more than one hour has elapsed since its preparation.

BURROUGHS WELLCOME & Co.

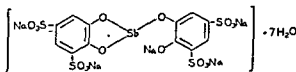
Neostam Stibamine Glucoside: 0.1, 0.2 and 0.5 Gm. vials. Each vial contains the stated quantity of stibamine glucoside hermetically sealed under nitrogen to preserve stability.

U. S. Trademark 503,747.

SALICINATE OF SODIUM

Sol.

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tains not less than 15.0 per cent and not more than 20.0 per cent of trivalent Sb, calculated on a moisture-free basis, the moisture being determined on a separate portion." *N. F.* The structural formula may be represented as follows:



For description and standards see The National Formulary
and Chemical Abstracts

after all evidence of the disease has disappeared. In schistosomiasis it is indicated together with iron as the treatment of choice in the intestinal stage of the disease. The iron salts should be given after the completion of the treatment and not concurrently. The anemia, when present, is apparently due to a prolonged iron deficiency.

Dosage—Intramuscularly (rarely intravenously), first day 15 cc., second day 35 cc., and on the third, fifth, seventh, ninth, eleventh, thirteenth and fifteenth days 5 cc., a total of 40 cc. of the 63 per cent solution. Following healing in a week or two weeks the course may be repeated and thereafter the drug is given once a week and then every fourteen days for several weeks to prevent relapse.

WINTHROP-STEARN'S, INC.

Solution Fuadin 35 cc. and 5 cc. ampuls. Each 1 cc. contains Fuadin, 63 mg., sodium bisulfite, not more than 0.125 per cent.

U. S. patents 1,549,154 (Aug. 11, 1925, expired) and 1,873,668 (Aug. 23, 1932, expires 1949). U. S. Trademark 304,950.

Arsenic Compounds

In some of the compounds listed in this chapter the arsenic is pentavalent, in others it is trivalent. A typical arsenic reaction results only from the trivalent arsenic, and in order to secure this action from those compounds containing pentavalent arsenic, their arsenic must be reduced to the trivalent form, this is done by the body, but the rate at which the reduction occurs varies greatly with the different compounds. In some cases, the desirable, as well as the undesirable, effects produced by these compounds are due to the arsenic which is slowly rendered active. In others the therapeutic effects may be due at least in part, to the unaltered molecules. The diseases in which arsenic therapy has proved useful are particularly those caused by protozoa. Inorganic arsenic will kill protozoa but it cannot be administered so as to reach the protozoa in fatal quantity. In the body, the organic compounds are less toxic to mammals and more toxic to protozoan parasites.

It is desired to kill, some are specifically etiotropic, that is they have a much greater affinity for the parasites causing the disease than they have for the tissues of the host.

Preparations of arsenic used intravenously come under the federal law covering serums, viruses, toxins and analogous products, and are subject to the same control.

COMPOUNDS CONTAINING TRIVALENT ARSENIC

According to Ehrlich's view, only trivalent arsenic is markedly toxic to microorganisms.

ness of these compounds and their limitations, and also the best methods of administering them, are still under discussion.

The toxic actions of arsphenamine are ascribed to the arsenic component in some cases. In other cases the decomposition of the solution has been assigned as a cause. Undoubtedly some reactions are due to idiosyncrasies on the part of the patient. However, there is seen a large group of these cases which must be explained otherwise. Certainly, improper technic in the preparation of the drug, as well as the improper (for example, too rapid) administration of the arsphenamine may add to the

where for the causation.

The water used should be, if possible, freshly distilled and freshly sterilized. All chemicals should be pure. Any rubber tubing employed for the first time should be soaked over night in 5 per cent sodium hydroxide solution, then boiled in distilled water and thoroughly washed with the same. Some reactions are undoubtedly due to administration of the drug to a patient on a full stomach or to one not properly prepared by previous catharsis. It is always well to start the use of arsenicals with a small dose—because of possible idiosyncrasies.

One should not be too much alarmed in a fresh case of syphilis.

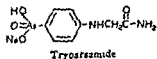
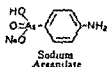
accentuation of the cutaneous and mucous membrane symptoms. One should be concerned, however, if with succeeding injections there are promptly recurring reactions in the form of gastritis,

rhagica, aplastic anemias, acute yellow atrophy and encephalitis.

The best treatment of these conditions is prophylaxis, and these drugs should never be readministered without inquiry of the patient and examination of the skin as to possible pruritus, jaundice, cutaneous eruptions, or other symptoms. Moreover, a

Arsphenamines are contraindicated or should be used with

infants Arsphenamine should not be used in beginning luetic optic neuritis until after some preliminary antiluetic therapy with either bismuth or mercury salts



Arsanilic acid is derived from arsenic acid $\text{AsO}(\text{OH})_3$ by replacing one hydroxyl by aniline (phenylamine) $\text{C}_6\text{H}_5\text{NH}_2$; related compounds are made by substituting derivatives of aniline

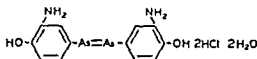
The compounds containing pentavalent arsenic are comparatively nontoxic when introduced into the animal system until changes take place that liberate the arsenic. When they are slowly decomposed, they produce favorable effects. If the reduction takes place with greater rapidity, they may produce ordinary arsenic poisoning.

Sodium cacodylate is excreted partly unchanged and partly as cacodylic oxide, which gives a foul odor to the breath, perspiration, etc. Further changes yield products containing inorganic, trivalent arsenic, by which the therapeutic effects, if there are any, are produced. It is not used in the treatment of syphilis.

Sodium arsanilate acts with especial violence on the optic nerve, producing optic atrophy, frequently resulting in permanent blindness. This may occur unfortunately even with therapeutic doses. It is not used in the treatment of syphilis.

Tryparsamide is a powerful trypanocide and only slightly treponemacidal. The drug, according to studies of Voegtlin and co-workers, when injected intravenously results in pronounced penetration of the nervous system tissue. This may explain its

ARSPHENAMINE-U. S. P.—3,3-Diamino-4,4-dihydroxy-arsenobenzene dihydrochloride dihydrate.—“Contains not less than 30 per cent and not more than 32 per cent of arsenic (As).” U. S. P. It complies with the requirements of the National Institute of Health, United States Public Health Service. The structural formula may be represented as follows:



For description and standards see the U. S. Pharmacopeia under Arspenamine.

Actions and Uses.—Arsphenamine is useful as a specific remedy for syphilis in all stages. According to available data, in incipient tabes, early paresis and cerebrospinal syphilis the drug can be employed with the prospect of most benefit in those cases in which its use is begun early.

The drug is used in the spirillum affections, such as relapsing fever and frambesia.

The remedy is contraindicated in severe disturbances of the circulatory organs, advanced degenerations of the central nervous system and cachexias, unless these are a direct result of syphilis; it is also contraindicated in patients who have pro-

Dosage.—Usually from 0.2 to 0.4 Gm.; though 0.6 Gm. may be given, the smaller doses are more extensively used.

For children from 0.1 to 0.2 Gm. In infants doses of from 0.02 to 0.1 Gm. may be used. The dose should be varied according to the strength and condition of the patient. The intravenous method is preferable and is to be recommended.

For intravenous injection one should proceed thus:

The ampul containing the drug is immersed in alcohol, in order to be sure that a cracked tube is not being used; then the tube is carefully v
and the contents s
each 0.1 gram of

meyer flask. The drug is allowed to dissolve with little or no agitation. Normal sodium hydroxide is then added to the solution, using 0.85 cc. to every 0.1 Gm. of the drug. Thus 0.6 Gm. of the drug would require 5.1 cc. of normal alkali. A precipitate of the base is first formed, which, after the contents are carefully agitated, is again brought into solution, the fluid being

strongly alkaline. Filter the alkalinized solution through sterile gauze, 4 ply, and dilute the filtrate with sterile distilled water.

should be mixed at once after opening, and under no circumstances should the contents of a tube damaged in transportation or any remnants of the powder from previously opened tubes be used. In all cases the skin should be disinfected with tincture of iodine or with alcohol.

MEACK & Co., Inc.

Arsphenamine: 0.1 Gm., 0.2 Gm., 0.3 Gm., 0.4 Gm., 0.5 Gm., 0.6 Gm., 1.0 Gm. and 3.0 Gm. ampuls

LFONATE—Bismuth—The sodium methylene sulfonic acid (the exact structural formula of which has not been established) with inorganic salts. It contains approximately 13 per cent of arsenic and 24 per cent of bismuth.

Preparation—

Bismuth arsphenamine sulfonate is prepared by adding a solution of potassium bismuth tartrate in water to an aqueous solution of 3,3'-diamino-4,4'-dihydroxy arsenobenzene N,N'-dimethylene sulfonate, dissolving the precipitate with a measured quantity of sodium hydroxide solution, precipitating by pouring the clear solution into a methyl alcohol-ether mixture and filtering off the precipitate and drying it in vacuo.

For tests and standards, see Section B.

Actions and Uses—For the treatment of syphilis. The drug is said to be somewhat slower in its action than intramuscularly administered sulfarsphenamine or intravenously administered neoarsphenamine. Some pain at the site of injection may be noted.

Dosage—0.2 Gm. A. intramuscularly 5 per cent butyn sulfate weekly doses may be later increased to biweekly doses in courses of treatment of twenty doses, or more.

ABBOTT LABORATORIES

Bismarsen: 0.1 Gm. and 0.2 Gm. ampuls, accompanied, respectively, by 1 cc. and 1½ cc. ampuls of a sterile, aqueous solution of 0.25 per cent butyn sulfate.

U. S. patent 1,603,891 (Nov. 2, 1926, expired) U. S. trademark 230,625.

U.
ch

ride, when dried in a vacuum desiccator over phosphorus pentoxide for twenty-four hours, contains not less than 25.3 per cent and not more than 27 per cent of total arsenic (As).—U. S. P. The structural formula may be represented as follows:



For description and standards see the U. S. Pharmacopeia under Dichlorophenarsine Hydrochloride.

Actions and Uses.—In recent literature may be found reports of an arsenical antisyphilitic agent which apparently was discovered in the early part of this century but was cast aside as being too toxic for clinical use. Some years later there were reports on its use in animals and in the treatment of amino-
[satis-
earlier
which

The preparations now available on the market contain sufficient alkaline buffering agent to make neutral a prepared solution for injection. They contain approximately 26 per cent of trivalent arsenic. On the addition of sterile distilled water to an ampul containing the mixture of dry dichlorophenarsine hydrochloride and alkaline buffer a reaction takes place, with the result that arsenoxide is supposed to be formed. It has been claimed that the latter agent is the therapeutically active part of the compound.

(A preliminary report of the Council appeared in THE JOURNAL, Sept. 25, 1943, p 208.)

Dosage.—Initial dose for adults 45 mg. (0.045 Gm.) intravenously. The second dose may be increased up to 68 mg. (0.068 Gm.). The maximum dose may be regarded as 68 mg. (0.068 Gm.). Injections may be given every four to five days, since the drug is excreted rapidly.

For children, the initial dose should not exceed 0.5 mg. per kilogram of body weight; the later doses should average between 0.5 mg. and 1.0 mg. per kilogram of body weight.

ABBOTT LABORATORIES

Dichlorophenarsine Hydrochloride: 45 mg. and 68 mg. ampuls and 0.45 Gm. and 0.68 Gm. multiple dose ampuls.

E. R. SQUIBB & SONS

Clorarsen: 45 mg. and 67 mg. ampuls and 0.45 Gm. and 0.67

Gm multiple dose ampuls. Each ampul contains the stated quantity of dichlorophenarsin hydrochloride admixed with three and one-third times its weight of a mixture containing sodium citrate 96 parts and sodium carbonate 4 parts

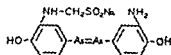
U. S. trademark 395,170.

WINTHROP-STEARNs, INC.

mg of sucrose.

0.102 Gm of sucrose

represented as follows.



For description and standards see the U. S. Pharmacopeia under Neoarsphenamine

Actions and Uses—Neoarsphenamine is a modified soluble compound of arsphenamine, its action and uses are those of arsphenamine. Neoarsphenamine and Metaphen have been proposed for the treatment of Vincent's Angina and stomatitis.

Dosage—Neoarsphenamine is probably less toxic than arsphenamine and, since it contains less arsenic, it is given in larger doses than arsphenamine. The average dose for a man is 0.45 to 0.60 Gm, with 0.45 Gm as the minimum and possibly 0.75 Gm as the maximum only for very large men. For women, 0.45 Gm is the average if the patient is about the normal in weight, 0.3 Gm would be the minimum and 0.6 Gm the maximum, the latter dose being given only to large women. Children may be given 0.1 to 0.2 Gm. The limit dose is 15 mg per kilogram of body weight. Here again a smaller dose is preferable.

Neoarsphenamine may be administered by intravenous or intramuscular injection, the former being considered decidedly preferable; the drug must not be administered subcutaneously.

For intravenous gravity injection, 12.5 cc. of freshly distilled water should be used for each 0.1 Gm. of neoarsphenamine.

Neoarsphenamine may be employed intravenously in concentrated solutions. For this purpose as much as 0.1 Gm. may be dissolved in 0.5 cc. of sterile freshly distilled water; the injection is made with a syringe instead of by gravity. It is well to draw out an equal amount of blood into the syringe containing the neoarsphenamine solution before reinjecting into the blood stream. It should be injected very slowly.

The ampul containing the drug is immersed in alcohol to detect a possible crack, then carefully wiped off; the neck filed across and broken off, and the contents sprinkled on the surface of cool, sterile distilled water and allowed to dissolve *without shaking* the solution. Any product incompletely soluble should be discarded. Solutions of neoarsphenamine must be injected *immediately* after their preparation. Neoarsphenamine must not be warmed and the temperature of the injected fluid should not be more than 20 to 22 C. (68 to 71.6 F.)

Neoarsphenamine may undergo deterioration in the ampule, and care should be exercised to use a drug of normal color and free solubility. The drug in fresh solution should be of canary
a cool dark

cc. of the
resultant so-

Caution—Solutions of Neoarsphenamine must be freshly prepared when required for use. The solution should not be shaken during its preparation.—U. S. P.

ABBOTT LABORATORIES

Neoarsphenamine: 0.45 Gm., 0.6 Gm. and 0.9 Gm.

Neoarsphenamine and Metaphen: Packages containing five ampules of neoarsphenamine, 40 mg. each, and one bottle of metaphen solution 1:1,000 (20 cc.).

MERCK & Co, INC.

Neoarsphenamine: 0.15 Gm., 0.3 Gm., 0.45 Gm., 0.6 Gm., 0.75 Gm., 0.9 Gm., 3.0 Gm. and 4.5 Gm. ampuls.

E. R. SQUIBB & SONS

Neoarsphenamine: 0.15 Gm., 0.3 Gm., 0.45 Gm., 0.6 Gm., 0.75 Gm., 0.9 Gm., 3.0 Gm. and 4.5 Gm. ampuls.

WINTHROP-STEARNs, INC.

Neosalvarsan: 0.15 Gm., 0.3 Gm., 0.45 Gm., 0.6 Gm., 0.75 Gm., 0.9 Gm., 1.5 Gm., 1.8 Gm., 3.0 Gm. and 4.5 Gm. ampuls.

U. S. trademark 88,862; 187,455.

OXOPHENARSINE HYDROCHLORIDE—U. S. P.—
Mapharsen (PARKE, DAVIS).—3-Amino-4-hydroxyphenylarsineoxide hydrochloride. "Oxophenarsine Hydrochloride, when

dried in a vacuum desiccator over phosphorus pentoxide for 24



For description and standards see The U S Pharmacopeia under Oxophenarsine Hydrochloride.

Actions and Uses—Oxophenarsine hydrochloride is proposed for the treatment of syphilis. It is stated to exhibit a relatively constant parasitocidal value. It is claimed to have a rapidly beneficial effect, particularly on early syphilis, causing the disappearance of spirochetes, healing of lesions and reversal of positive Wassermann reactions in a large percentage of cases. The reactions following the use of oxophenarsine hydrochloride are less severe than those observed after the use of the arsphenamines.

Dosage—Intravenously, 0.03 Gm for women and 0.04 Gm for men, initially. The dose may be increased at the second injection to 0.04 Gm. for women and 0.06 Gm. for men. The maximum dose which should not be given any patient at the first injection, may be regarded as 0.06 Gm. Injections may be given every four or five days, since it is excreted very rapidly from the body. For children the initial dose should not exceed

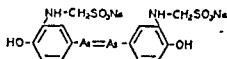
PARKE, DAVIS & COMPANY

Mapharsen: 40 mg and 60 mg ampuls

Mapharsen: 0.6 Gm multiple dose ampuls. *Caution: These ampuls are hospital packages and represent either 10 doses at 60 mg or 15 doses at 40 mg.* Each of the ampuls of mapharsen contains the stated amount of the arsenical, oxophenarsine hydrochloride admixed with anhydrous sodium carbonate, 4.3 per cent and anhydrous sucrose, 81.4 per cent.

U S patents 2,092,028 and 2,092,036 (Sept 7, 1937, expires 1954), 2,221,817 (expires Nov 19, 1947) and 2,230,132 (expires April 21, 1959).
U S trademark 299,173

It complies with the requirements of the National Institute of Health of the United States Public Health Service. The structural formula may be represented as follows:



For description and standards see the U. S. Pharmacopeia under Sulfarsphenamine.

Actions and Uses.—The same as those of neoarsphenamine; it is probably somewhat more stable in solution in the presence of air, and it permits of intramuscular injection. In terms of percentages there seems to be a higher incidence of reactions following the use of sulfarsphenamine, far more, in fact, than after the use of the other arsenicals employed in the treatment of syphilis. These reactions consist in (a) dermatitis, (b) hemorrhagic eruptions, (c) meningo-vascular reactions, and (d) aplastic anemias. All patients under treatment with sulfarsphenamine should be followed closely by the physician for evidence of reaction. The drug has a place, and may be used by the intramuscular route in the treatment of early heredo-syphilis and in certain cases where the patient has such poor veins that intravenous therapy is out of the question.

Dosage.—The maximum dosage by any route should probably not exceed 0.4 Gm., or at most 0.5 Gm. of the dry substance.

For intramuscular or subcutaneous use the drug is dissolved in sterile, freshly distilled water in the proportion of about 0.1 Gm. to 0.3 cc., the total volume being not more than 1.0 to 2.0 cc. There is probably less local reaction where a minimum of diluent is employed. For intravenous use the drug should be diluted in the proportion of 0.1 Gm. to not less than 1.0 and preferably, 4.0 cc., or more, the total volume amounting to 5.0 to 20.0 cc. or more. Dosage for infants is 10 mg. to 15 mg. per kilogram of body weight.

ABBOTT LABORATORIES

Sulfarsphenamine: 0.1 Gm., 0.2 Gm., 0.3 Gm., 0.4 Gm. and 0.6 Gm. ampuls.

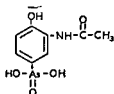
MERCK & CO., INC.

Sulfarsphenamine: 0.1 Gm., 0.2 Gm., 0.3 Gm., 0.4 Gm., 0.5 Gm. and 0.6 Gm. ampuls

COMPOUNDS CONTAINING PENTAVALENT ARSENIC

ACETARSONE-N. F.—Stovarsol (MERCK).—3-Acetyl-amino-4-hydroxyphenylarsonic acid.— $\text{C}_8\text{H}_{10}\text{O}_5\text{AsN}$.—"When

dried over sulfuric acid for 3 hours, contains not less than 26.9 per cent and not more than 27.6 per cent of As [arsenic] "—N. F.



For description and standards see The National Formulary under Acetarsonsone and Acetarsonsone Tablets

Actions and Uses—Acetarsonsone has been reported to produce favorable effects in the treatment of amebiasis. Acetarsonsone is useful as a means of medication of the vagina in the treatment of *Trichomonas vaginitis*. Its use in the treatment of sarcoid has been recommended by various dermatologists. Acetarsonsone has been proposed for use both in prophylaxis and in treatment in certain cases of syphilis, but the evidence is thus far inconclusive. Its use in amebic infections undoubtedly is of value, though still in the experimental stage. In using acetarsonsone, the physician should remember that he is working with a rather toxic arsenical preparation, which may give rise to gastrointestinal symptoms and hepatitis as well as to the same cutaneous disturbances that are found with the arsphenamines, for example, urticaria, erythema of various types and even hemorrhagic eruptions. At the least sign of intolerance the physician should discontinue the use of the drug for the time being.

Acetarsonsone in common with other arsenicals, should ordinarily not be employed in the presence of hepatitis or kidney damage. Excretion of the administered arsenic is relatively slow, suitable rest periods must therefore be interposed in the treatment to prevent cumulative effects.

The diagnosis of amebiasis depends on the observation of motile forms or cysts of *Endamoeba histolytica* in stool specimens (repeated examinations are often necessary) or their recovery by means of the proctoscope from the intestinal mucosa, positive diagnosis can often be made by the latter procedure when stool examinations are negative, and this is considered to be the more satisfactory as well as the more rapid method of diagnosis in many cases.

In view of the frequency of persistent infection in the absence of marked symptoms, adequate therapy includes reexaminations and repetitions of courses of treatment.

Dosage—Orally, 0.25 Gm. for adults, two or three doses a day for a period of 10 days.
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 vagina a p
 ture of eq
 dose 4 Gm.—1 teaspoonful of the mixture containing 0.5 Gm

acetarsone. In case of pregnancy, if insufflation is employed, care must be taken to exert no positive pressure in the vagina.

Intravaginally, one tampon tablet every other day or daily, followed by a mildly acid douche after a third treatment or after a week's treatment, has been reported to give satisfactory results.

ALLEN LABORATORIES, INC.

Allen Brand Tampon with Acetarsone (Stovarsol): A lightly compressed stitched tampon of absorbent cotton, coated with 0.1 Gm. of powdered acetarsone, to which is attached a tablet consisting of acetarsone 32 mg. in a tablet base composed of lactose, dextrose, boric acid and starch with a small quantity of sodium bicarbonate and tartaric acid to aid disintegration.

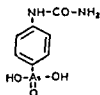
MERCK & Co., INC.

Stovarsol (Powder).

Tablets Stovarsol: 25 mg., 50 mg. and 100 mg.

U. S. trademark 177,082.

CARBARSONE-U. S. P.—4-Ureidophenylarsonic acid.—"When dried at 80 C for six hours, contains not less than 28.1 and not more than 28.8 per cent arsenic (As)."—U. S. P. The structural formula may be represented as follows:



For description and standards see the U. S. Pharmacopeia under Carbarsone and The National Formulary under Carbarsone Tablets.

Actions and Uses.—Carbarsone is proposed for the treatment of intestinal amebiasis. It is administered usually by mouth; in acute amebic dysentery or in resistant cases with motile amebas in the stools, retention enemas may be employed. While carbarsone is said to be less toxic than acetarsone and serious untoward effects appear to be uncommon, cutaneous disturbances and other reactions common to arsenic compounds have been observed. It has been suggested that owing to its chemical structure (in which a modified amido group is para to the arsenic atom, similar to the arrangement in tryparsamide) the administration of carbarsone may lead to injury of the optic nerve. While visual disturbances appear to be quite rare, the possibility of their occurrence should nevertheless be kept in mind during the therapeutic use of the drug. A moderate increase in intestinal activity may be observed. Carbarsone, in common with other arsenicals, should ordinarily not be employed in the

presence of hepatitis or kidney damage. Excretion of the administered arsenic is relatively slow, suitable rest periods must therefore be interposed in the treatment to prevent cumulative effects.

The diagnosis of amebiasis depends on the observation of motile forms or cysts of *Endamoeba histolytica* in stool specimens (repeated examinations are often necessary) or their recovery by means of the proctoscope from the intestinal mucosa, positive diagnosis can often be made by the latter procedure when stool examinations are negative and this is considered to be the more satisfactory as well as the more rapid method of diagnosis in many cases.

In view of the frequency of persistent infection in the absence of marked symptoms, adequate therapy includes reexaminations and repetitions of courses of treatment.

Dosage—Orally for adults the usual dose is 0.25 Gm twice a day for ten days. If necessary this may be repeated following a ten day rest period. For children the dosage may be reduced according to weight. As retention enemas for adults 2 Gm. of the drug dissolved in 200 cc of warm 2 per cent sodium bicarbonate solution may be administered following a cleansing alkaline enema every other night for a maximum of five doses if necessary. Because of the large dosage employed (a total of 10 Gm over a period of nine days) oral administration should be interrupted during this interval.

ELI LILLY AND COMPANY

Carbarsone (Powder) 2 Gm vial

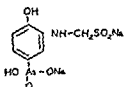
Pulvules Carbarsone 0.25 Gm

Suppositories Carbarsone 0.13 Gm

Tablets Carbarsone 50 mg and 0.25 Gm.

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For tests and standards see Section B

Actions and Uses.—Phenarsone sulfoxylate, a pentavalent arsenical, may be used in the treatment of *Trichomonas vagi-*

against untoward reactions. Such reactions include dermal and hemopoietic changes, nitritoid reactions. Since phenarsone sulfoxylate is a pentavalent arsenic compound, every care should be exercised and visual and color field examinations made prior to drug therapy so that contraction of visual field or symptoms of blurring may be observed.

Dosage.—For the treatment of syphilis of the central nervous system, 1 Gm. of phenarsone sulfoxylate dissolved in 10 cc. of sterile distilled water, administered intravenously once a week. The injections may be given continuously for periods of forty to fifty weeks. Concurrent bismuth therapy may be employed during a portion of the course of phenarsone sulfoxylate injection. Phenarsone sulfoxylate may be given as a supplement to fever therapy in the treatment of various forms of central nervous system syphilis.

For the treatment of *Trichomonas vaginalis*, phenarsone sulfoxylate may be administered by insufflation of the powder (with kaolin) and in the form of a suppository. For insufflation the vaginal tract and external os of the cervix are thoroughly cleansed and dried; then the contents of a 3 Gm. vial of phenarsone sulfoxylate with kaolin are introduced by an insufflator. A cautionary statement is issued on the use of positive pressure in the pregnant female when insufflation is employed. The escape of air from the vagina should be permitted during compressions in case the patient is pregnant. The patient is treated for three consecutive days. Then additional treatments are given at three day intervals. No douche should be taken during the treatment.

Phenarsone sulfoxylate suppositories may be used in conjunction with insufflation. They offer a way of providing phenarsone sulfoxylate between insufflation treatments. Suppository treatment is started no sooner than twenty-four hours after the last power treatment. One is inserted every second or third night until the patient reports for the next insufflation treatment. They may also be used alone by insertion of one suppository every third or fourth night for not more than three weeks. The patient should be warned against prolonged use of this treatment without the advice of a physician, since an arsenical is being employed. Suppositories alone should not be expected to produce permanent results: merely to lessen the discharge and diminish symptoms.

ABBOTT LABORATORIES

Aldarsone (Powder): 0.5 Gm. and 1 Gm. ampuls.

Aldarsone with Kaolin: 30 Gm. Each 30 Gm. contains phenarsone sulfoxylate 0.5 Gm. and kaolin 2.5 Gm. packaged in glass tubes suitable for use with insufflator.

days. In such cases treatment with tryparsamide should be discontinued, the visual fields determined at least weekly for three to four weeks, and then, if there is no evidence of damage to the optic nerve, the injection resumed, using great caution, minimal dosage at first, and checking the visual field preceding each injection. The drug is said to "have no virtues in ophthalmic syphilis."

Dosage.—From 1.0 to 3.0 Gm. for adults, depending on the purpose for which the drug is used. In general, the dose should not exceed 0.04 to 0.05 Gm. per kilogram of body weight, and such doses should not be repeated at intervals of less than one week. Tryparsamide is employed by the intravenous route. The drug is dissolved in sterile water or physiologic solution of sodium chloride. Tryparsamide should never be administered by mouth.

MERCK & Co., Inc.

Tryparsamide (Powder): 50 Gm bottle and 1 Gm, 2 Gm. and 3 Gm. ampuls.

U. S. patents 1,280,119, 1,280,120, 1,280,121, 1,280,122, 1,280,123, 1,280,124 and 1,280,126 (Sept. 24, 1918; expired) by license of the Rockefeller Institute for Medical Research. U. S. trademark 186,022 (expired).

Bismuth Compounds

Until 1921 bismuth had been used particularly in the treatment of intestinal infections, as a paste for tuberculous fistulae and in radiology. Sauton and Robert then showed the value of sodium

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realized more and more and its general use has been increased enormously throughout the world. Bismuth seems to have both

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the reason that the therapeutic dose approaches too closely to the toxic dose. The compounds employed for intramuscular injection consist of water soluble salts dissolved in aqueous solu-

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a

soluble preparations are claimed to be more exact in their dosage and to be absorbed more rapidly than insoluble suspensions of

bismuth salts. They are said not to be absorbed and excreted so rapidly as the soluble bismuth preparations. Thus, they combine some of the advantages of both the soluble and of the

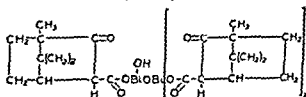
should hold the syringe loosely between the thumb and first finger, much like holding a pencil. The skin of the buttock is

mine. The present evidence appears to show that there is warrant for the administration of bismuth compounds in the treatment of syphilis in connection with arsphenamine or as a substitute for mercury therapy. Some few syphilologists use bismuth therapy alone in treatment of syphilis. These men are much in the minority, however. Bismuth compounds are most valuable in the treatment of syphilis in patients who are intolerant to other drugs or who show resistance to other drugs used in syphilis, e.g., the arsenic-fast individual, or so-called arsenic-intolerant individual. However, there is far more chance of curing a patient with syphilis where the physician is able to use both arsenical therapy and bismuth therapy, either in alternating courses or, in certain instances, in a combined fashion. Treatment with bismuth preparations is not usually injurious if the necessary precautions are taken (careful observation of the skin for untoward reaction, of the mouth for signs of beginning bismuth stomatitis and of the urine for evidence of irritation of the kidneys).

superior to either the arsenicals or bismuth in the treatment of neurosyphilis. It is as yet too early to state the precise relative therapeutic efficacy of the various agents employed in this condition, but all are considered to be of value.

In common with another heavy metal, mercury, bismuth preparations when administered by injection, have a definite diuretic action. Excretion studies of various bismuth compounds used in the treatment of syphilis give some indications as to the best type of bismuth salts for desired results. The usefulness of a bismuth preparation involves the concentration of active bismuth attained in the tissues, especially in the blood, and the height, course, rise, duration and decline of this concentration. As a rule, water solutions, if repeated often enough, give a rapid and important absorption of the metal and a sustained high concentration in the blood stream. This can be kept up if the injections are given frequently enough, i.e., two or three times a week. Oil suspensions differ in that there is a slower absorption and concentration in the blood stream, but one which persists longer, thus requiring injections but once a week. Certain of the oil solutions have like characteristics, with an added more rapid absorption than the oil suspension. Bismuth subsalicylate is more slowly absorbed and there is a somewhat longer delay before the bismuth effect is achieved. Moreover, in small amounts it continues to be excreted over long periods of time, even months after injections are stopped. Whether this long excretion indicates a therapeutic level of the drug in the body is doubtful.

BISMUTH CAMPHOCARBOXYLATE.—Bismo-Cymol (Abbott).—A basic bismuth salt of camphocarboxylic acid (camphor-3-carboxylic acid) having the probable structural formula shown below. It contains between 37 and 40 per cent of bismuth. The formula may be represented as follows:



For tests and standards, see Section B

Actions and Uses.—Bismuth camphocarboxylate is proposed as a means of obtaining the systemic effects of bismuth in the treatment of syphilis (see article on Bismuth Compounds). Bismuth camphocarboxylate belongs to the class of so-called liposoluble bismuth compounds which, because of their solubility, are absorbed more rapidly than insoluble bismuth salts, approaching that of soluble bismuth salts. Though animal experiments seem to show a low toxicity for this preparation, in human beings it is well to watch the gums closely for evidence of beginning stomatitis.

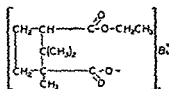
Dosage—Bismuth camphocarboxylate is injected intramuscularly in doses representing 0.1 Gm. of metallic bismuth once a week or in doses representing 50 mg of metallic bismuth twice a week for from eight to ten weeks

ABBOTT LABORATORIES

Solution Bismo-Cymol: 60 cc ampuls Each cc contains bismo-cymol equivalent to 50 mg of metallic bismuth, dissolved in olive oil.

U. S. patent 1,921,638 (Aug. 8, 1933, expires 1950) U. S. trademark 277,960

BISMUTH ETHYL CAMPHORATE



For tests and standards, see Section B

It may be prepared by the interaction of sodium ethylcamphorate and bismuth nitrate in dilute aqueous glycerin solution. The product may then be extracted with chloroform and recovered by the removal of that solvent.

little local reaction

Dosage—For the average adult, 2 cc. (80 mg. of metallic bismuth), administered once a week for a series of ten to fifteen injections

THE UPJOHN COMPANY

Solution Bismuth Ethylcamphorate in Oil with Benzyl Alcohol 2.5%: 1 cc and 2 cc ampuls and 30 cc. vials Each cubic centimeter of solution contains a suspension of bismuth ethylcamphorate equivalent to 40 mg of elemental bismuth, camphor 0.10 Gm. and benzyl alcohol 0.025 cc, dissolved in vegetable oil.

BISMUTH POTASSIUM TARTRATE-U. S. P.—Potassium Bismuth Tartrate—"Contains the equivalent of not less than 60 per cent and not more than 64 per cent of Bi [bismuth]." —U. S. P.

For description and standards see the U. S. Pharmacopeia under Bismuth Potassium Tartrate and Bismuth Potassium Tartrate Injection.

Actions and Uses.—It is used for the antisyphilitic effects of bismuth. See general article, Bismuth Compounds.

Dosage.—(a) Oily Suspension.—From 0.1 to 0.2 Gm. by intramuscular injection, preferably into the gluteal muscle. The injections may be repeated at intervals of seven days until a total of from 2.4 to 3.0 Gm. has been given. (b) Aqueous Isotonic Solution.—50 mg. by intramuscular injection, preferably into the gluteal muscles, three times a week, until a total of 12 to 18 injections has been given.

ABBOTT LABORATORIES

Suspension Bismuth Potassium Tartrate in Oil 10% with Butyn 0.4%: 60 cc. bottle. Each cc. contains Bismuth potassium tartrate 0.1 Gm. (equivalent to 62 mg. elemental bismuth), Butyn 0.4 per cent and Metaphen 1:20,000 suspended in peanut oil.

BREWER & Co., Inc.

Solution Bismuth Potassium Tartrate: 2 cc. ampuls. Each ampul contains bismuth potassium tartrate 50 mg. with benzyl alcohol 0.04 Gm.

BISMUTH SODIUM TARTRATE.—A basic sodium bismuth tartrate containing from 72.7 to 73.9 per cent of bismuth.

For tests and standards, see Section B.

Actions and Uses.—Bismuth sodium tartrate is proposed as a means of obtaining bismuth in the treatment of syphilis (see Bismuth Compounds). The drug has a

Dosage.—30 mg. by intramuscular injection, preferably into the gluteal muscle. The initial dose is 15 mg., increased to 30 mg. with the second dose and continued in three doses weekly for from six to ten weeks.

G. D. SEARLE & Co.

Solution Bismuth Sodium Tartrate, 1.5% with Benzyl Alcohol 2%: 2 cc. ampul and 60 cc. vial. An aqueous solution containing bismuth sodium tartrate 30 mg., benzyl alcohol 40 mg. and sucrose 0.25 Gm., in 1 cc.

Solution Bismuth Sodium Tartrate, 3% with Benzyl Alcohol 2%: 2 cc. ampuls and 60 cc. vial. An aqueous solution containing bismuth sodium tartrate 30 mg., benzyl alcohol 20 mg. and sucrose 0.25 Gm., in one cubic centimeter.

U. S. patents 1,663,201 (March 20, 1928; expired), and 1,801,433 (April 21, 1931; expires 1948).

BISMUTH SODIUM THIOGLYCOLLATE—Thio-
(PARKE, DAVIS).—Bismuth sodium thioglycollate.—A

tests and standards, see Section B

Uses and Uses—Bismuth sodium thioglycollate is proposed
means of obtaining the systemic effects of bismuth in the

malaria.

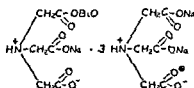
Dose—For the average adult, 0.2 Gm administered intra-
rarily three times a week for a series of from twelve to
doses

DAVIS & COMPANY

-Bismol: 0.2 Gm and 2 Gm ampuls

trademark 220,808

may be represented as follows



tests and standards, see Section B

Uses and Uses—Bismuth sodium thioglycollate is designed

malaria.

BISMUTH POTASSIUM TARTRATE-U. S. P.—Potassium Bismuth Tartrate—"Contains the equivalent of not less than 60 per cent and not more than 64 per cent of Bi [bismuth]." —U. S. P.

For description and standards see the U. S. Pharmacopeia under Bismuth Potassium Tartrate and Bismuth Potassium Tartrate Injection

Actions and Uses.—It is used for the antisyphilitic effects of bismuth. See general article, Bismuth Compounds.

Dosage.—(a) Oily Suspension—From 0.1 to 0.2 Gm. by intramuscular injection, preferably into the gluteal muscle. The injections may be repeated at intervals of seven days until a total of from 2.4 to 3.0 Gm. has been given. (b) Aqueous Isotonic Solution.—50 mg. by intramuscular injection, preferably into the gluteal muscles, three times a week, until a total of 12 to 18 injections has been given.

ABBOTT LABORATORIES

Suspension Bismuth Potassium Tartrate in Oil 10% with Butyn 0.4%: 60 cc. bottle. Each cc. contains Bismuth potassium tartrate 0.1 Gm. (equivalent to 62 mg. elemental bismuth), Butyn 0.4 per cent and Metaphen 1:20,000 suspended in peanut oil.

BREWER & Co, INC.

Solution Bismuth Potassium Tartrate: 2 cc. ampuls. Each ampul contains bismuth potassium tartrate 50 mg. with benzyl alcohol 0.04 Gm

BISMUTH SODIUM TARTRATE.—A basic sodium bismuth tartrate containing from 72.7 to 73.9 per cent of bismuth.

For tests and standards, see Section B.

Actions and Uses.—Bismuth sodium tartrate is proposed as a means of obtaining the systemic effects of bismuth in the treatment of syphilis (See general article, Bismuth Compounds). The drug has a definite diuretic action.

Dosage.—30 mg by intramuscular injection, preferably into the gluteal muscle. The initial dose is 15 mg., increased to 30 mg. with the second dose and continued in three doses weekly for from six to ten weeks

G. D. SEARLE & Co.

Solution Bismuth Sodium Tartrate, 1.5% with Benzyl Alcohol 2%: 2 cc ampul and 60 cc. vial. An aqueous solution containing bismuth sodium tartrate 30 mg., benzyl alcohol 40 mg and sucrose 0.25 Gm., in 1 cc.

Solution Bismuth Sodium Tartrate, 3% with Benzyl Alcohol 2%: 2 cc ampuls and 60 cc. vial. An aqueous solution containing bismuth sodium tartrate 30 mg., benzyl alcohol 20 mg. and sucrose 0.25 Gm., in one cubic centimeter.

U S patents 1,663,201 (March 20, 1928; expired), and 1,801,433 (April 21, 1931; expires 1948).

BISMUTH SODIUM THIOGLYCOLLATE—Thio-Bismol (PARKE, DAVIS)—Bismuth sodium thioglycollate—A salt formed by the interaction of sodium thioglycollate and bismuth hydroxide. The product has the general formula $\text{Bi}(\text{SCH}_2\text{CO}_2\text{Na})_3$ though it may differ slightly in composition from this formula. It contains approximately 38 per cent of bismuth.

For tests and standards see Section B

peptic malaria.

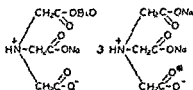
Dosage—For the average adult, 0.2 Gm administered intramuscularly three times a week for a series of from twelve to fifteen doses

PARKE, DAVIS & COMPANY

Thio-Bismol—0.2 Gm and 2 Gm ampuls

U. S. trademark 229 608

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if sodium
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For tests and standards, see Section B

Actions and Uses—Bismuth sodium triglycollamate is designed to provide bismuth in a form effective for oral administration in the treatment of syphilis. It may be used as an adjunct with arsenicals or other agents shown to be effective in the treatment of the disease. It may be used in the treatment of certain forms of peptic ulcer, for curative treatment of primary and secondary syphilis, and in other forms of infection.

It may be used in the treatment of certain forms of peptic ulcer, for curative treatment of primary and secondary syphilis, and in other forms of infection.

Dosage.—Bismuth sodium triglycollamate is administered orally in tablet form, usually prescribed in single doses of 0.41 Gm. (75 mg. of bismuth) two or three times daily after meals to provide a total daily dosage of from 0.82 Gm. (150 mg. of bismuth) to 1.23 Gm. (225 mg. of bismuth). The higher total daily dosage is desirable to maintain a satisfactory bismuth excretion level, but this may be temporarily reduced to the lower figure to overcome gastro-intestinal disturbances that are occasionally encountered.

CARROLL DUNHAM SMITH PHARMACAL CO.

Tablets Bistrimate: 0.41 Gm Each tablet contains the equivalent of 75 mg of bismuth

U. S. patent 2,348,984.

BISMUTH SUBSALICYLATE-U. S. P.—Basic Bismuth Salicylate—"A basic salt, which, when dried over sulfuric acid for 18 hours, yields upon ignition not less than 62 per cent and not more than 66 per cent of Bi_2O_3 ."—U. S. P. The structural formula may be represented as follows:



For description and standards, see the U. S. Pharmacopeia under Bismuth Subsalicylate and Bismuth Subsalicylate Injection

Actions and Uses.—The oral administration of bismuth subsalicylate has apparently found little application, and it is probably decomposed in part with the liberation of salicylic acid in the presence of the gastric juice. Its chief use is in the treatment of syphilis for which purpose it is suspended in oil and is injected intramuscularly. It is absorbed slowly and irregularly after intramuscular injection and is excreted mainly through the kidney. The rate of elimination following a single intramuscular dose reaches the maximum in about 11 or 12 days, and with repeated intramuscular injections the maximum is reached in about 19 to 21 days, after which the rate of excretion remains fairly constant for some time. See general article, Bismuth Compounds.

Dosage.—Gastro-intestinal, 1 Gm. Antisyphilitic, by parenteral injection, 0.125 Gm. The drug is suspended in oil and injected intramuscularly once a week until (a course of) from eight to twelve doses have been injected.

ABBOTT LABORATORIES

Suspension Bismuth Subsalicylate in Oil with Chlorobutanol 3%: 1 cc. ampuls; 30 cc. and 60 cc. bottles. A suspension of bismuth subsalicylate in a mixture of peanut oil and ethyl esters of olive oil fatty acids containing in each cubic centimeter 0.13 Gm of bismuth subsalicylate and chlorobutanol 3 per cent.

DIARSENOL COMPANY, INC.

Suspension Bismuth Subsalsicylate in Oil with Chlorobutanol 3%: 30 cc, 60 cc, and 100 cc bottles. A suspension of bismuth subsalsicylate in peanut oil, each cubic centimeter containing 0.13 Gm of bismuth subsalsicylate (equivalent to 75 mg of Bi metal) and 30 mg, (3 per cent) of chlorobutanol.

ENDO PRODUCTS, INC.

Suspension Bismuth Subsalsicylate in Oil with Chloro-

Suspension Bismuth Subsalsicylate in Oil with Chlorobutanol 3%: 20 cc, 60 cc and 100 cc. bottles. A suspension of bismuth subsalsicylate in peanut oil containing in each cubic centimeter bismuth subsalsicylate U S P equivalent to 50 milligrams to 60 milligrams of bismuth with 3 per cent chlorobutanol.

MERCK & Co, INC

Bismuth Subsalsicylate (Powder): Bulk.

PARKE, DAVIS AND COMPANY

Suspension Bismuth Subsalsicylate in Oil with Chlorobutanol

0.13 Gm

Suspension Bismuth Salicylate in Oil with Chloretone 3%: 0.13 Gm. in 1 cc ampuls. Each ampul contains 1 cc of a suspension of bismuth subsalsicylate 0.13 Gm, in peanut oil, containing 3 per cent of chlorobutanol.

THE SMITH-DORSEY Co

Suspension Bismuth Subsalsicylate in Oil with Chlorobutanol 3%: 50 cc vials. A suspension of bismuth subsalsicylate in peanut oil containing in each cubic centimeter bismuth subsalsicylate 0.13 Gm with 3 per cent chlorobutanol added.

THE UPJOHN COMPANY

Suspension Bismuth Subsalsicylate in Oil with Chlorobutanol 3%: 50 cc vials. Each cubic centimeter contains 0.13 Gm of bismuth subsalsicylate and 30 mg of chlorobutanol.

21 per cent bismuth (Bi), 62 per cent iodide (I-) and 11 per cent water of hydration.

For tests and standards, see Section B.

Actions and Uses.—It is claimed for iodobismuthite sodium that it has the quality of appearing in the spinal fluid and of penetrating the brain tissue. This claim and therapeutic indications based upon it require further confirmation.

Dosage.—See Iodobismutol with Ethyl Aminobenzoate.

IODOBISMUTHITE SODIUM WITH ETHYL AMINOBENZOATE.—Iodobismutol with Benzocaine (SQUIBB).—A solution of sodium iodobismuthite (bismuth sodium iodide) and sodium iodide in propylene glycol containing ethyl aminobenzoate.

For tests and standards, see Section B.

Actions and Uses.—Iodobismuthite sodium with ethyl aminobenzoate seems to be well absorbed and to be excreted fairly

.....

Dosage.—Intramuscular injections of 2 cc. repeated every three days. Two full days should elapse between injections. From sixteen to twenty injections comprise a course of treatment. In case of arsenical sensitization such therapy may be continued over a long period of time. At each injection the

..... oxide,

E. R. SQUIBB & SONS

Solution Iodobismutol with Benzocaine: 2 cc. ampuls and 50 cc. rubber capped bottles. Each 2 cc. contains iodobismuthite sodium 0.12 Gm., sodium iodide 0.24 Gm., ethyl aminobenzoate 80 mg., propylene glycol q. s. 2 cc.

U. S. patent 1,927,210 (Sept. 19, 1933; expires 1950).

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For tests and standards, see Section B.

Actions and Uses.—Potassium sodium bismuthyl tartrate is proposed as a means of obtaining the systemic effects of bismuth in the treatment of syphilis (See general article, Bismuth Compounds).

QUININE BISMUTH IODIDE.—A substance of variable composition containing between 18 and 20.1 per cent of bismuth, between 48.7 and 53.5 per cent of iodine; and quinine.

For tests and standards, see Section B.

Actions and Uses.—Quinine bismuth iodide is proposed as a

means of obtaining the systemic effect of bismuth in the treatment of syphilis (See general article Bismuth Compounds)

SOBISMINOL MASS—A complex organic bismuth product the chemical nature of which has not been fully established. It is obtained by the interaction of sodium bismuthate, *triso*-propanolamine and propylene glycol. It contains between 19.25 and 20.25 per cent of bismuth, 0.75 Gm. of sobisminol mass represents 150 mg. of bismuth.

For tests and standards see Section B

Actions and Uses—Sobisminol mass is proposed in the treatment of syphilis and is intended for use by the oral route. It is particularly indicated for those patients unable to undergo intramuscular bismuth therapy and to supplant therapy by that route for patients compelled for a time to be out of contact with their physician. Again it may be indicated in certain other types of syphilis, e.g. congenital and latent syphilis. It is to be emphasized that it is too dangerous a drug to be employed by the patient without the careful supervision and direction of his physician and it is sold only on prescription. In the first few days of therapy the patient should be carefully supervised and later watched for evidence of gastro intestinal upsets and of bismuth intoxication.

Absorption of sobisminol (mass or solution) appears to be rapid and sufficient to maintain an effective antisypilitic level of bismuth concentration in the body. An adequate amount of sobisminol mass by mouth can be expected to result in a curve for urinary excretion resembling closely in course and degree those given by intramuscular injection of the water soluble and oil soluble compounds. The oral dose has to be considerably higher than the intramuscular dose of sobisminol. Further, intramuscular injections of sobisminol solution results in greater urinary excretion than is obtained by oral administration. Daily urinary excretion of bismuth compounds fluctuates considerably, but excretion continues for many days.

The toxicity of sobisminol compares favorably with that of other water soluble bismuth compounds used in the treatment of syphilis. Side effects appear to be usually of a relatively transient nature. They include nausea, vomiting, burning sensations in the esophagus, diarrhea, stomatitis and bismuth line. There appears to be no tendency to cumulative toxic effects.

Dosage—Adult dosage from two to three capsules three times a day, taken with plenty of water at 10 a. m., 3 p. m. and 8 p. m. Each capsule represents 150 mg. of metallic bismuth. Unless contraindications arise such therapy may be continued for from ten to twelve weeks and represents a course of bismuth therapy. For children the dosage may be cut down to one capsule three times a day, or a 75 mg. capsule three times a day for a young child.

ELI LILLY AND COMPANY

Pulvules Cobisminol Mass 0.75 Gm.

Chiniofon

sented as follows:



For description and standards see the U. S. Pharmacopeia under Chiniofon and Chiniofon Tablets.

Actions and Uses.—Chiniofon, which is closely similar to preparations introduced under various proprietary names as wound antiseptics, has been found to be of use in the treatment of amebic dysentery. It is claimed that the action of the drug is probably due to its absorption and direct action through the blood stream on the amebas invading the bowel wall. The drug has been reported in some cases to produce diarrhea; but serious toxic effects do not appear to be common.

The diagnosis of amebiasis depends on the observation of motile forms or cysts of *Endameba histolytica* in stool specimens (repeated examinations are often necessary) or their recovery by means of the proctoscope from the intestinal mucosa; positive diagnosis can often be made by the latter procedure when stool examinations are negative, and this is considered to be the more satisfactory as well as the more rapid

of marked symptoms, adequate therapy includes reexaminations and repetitions of courses of treatment.

Dosage.—Orally, for adults, from 0.25 to 1.0 Gm. in the form of pills, cachets or solutions, three times daily; for children, according to age; rectally, 1 to 5 Gm. freshly dissolved in 200 cc. of water at a temperature not exceeding 44 C. The course of treatment requires from seven to fourteen days. Combined oral and rectal administration has been used in acute cases and in the more serious chronic cases accompanied by obstinate clinical symptoms. It has been pointed out that the iodine content of chiniofon should be considered when chronic endamebiasis is accompanied by thyroid disturbance.

Until more evidence becomes available, chiniofon should be used with caution in cases with liver damage.

ABBOTT LABORATORIES

Enterab Tablets Chiniofon: 0.25 Gm. Each tablet is enteric

coated with a resin prepared from stearic acid phthalic anhydride and glycerin

U S trademark 153 674

ERNST BISCHOFF Co

Anayodin (*Powder*) 25 Gm and 100 Gm bottles

Pills Anayodin 0.25 Gm enteric coated with shellac and magnesium stearate

U S trademark 232 215

ENDO PRODUCTS INC.

Chiniofon (*Powder*) 30 Gm bottles

Tablets Chiniofon (*Enteric Coated*) 0.25 Gm

PREMO PHARMACEUTICAL LABORATORIES INC.

Chiniofon Enerels 0.25 Gm tablets coated with shellac.

WINTHROP STEARNS INC.

Chiniofon (*Powder*) Bulk

Tablets Chiniofon 0.25 Gm The tablets are coated with keratin

Iodine Compounds

DIIDO HYDROXYQUINOLINE — Diodoquin (SEARLE) — Yodoxin (LEMKE) — 5.7 di Iodo 8 hydroxyquinoline $C_9H_4NOH I_2$ — A compound resulting from the introduction of two atoms of iodine into 8 hydroxyquinoline. The structural formula may be represented as follows



For tests and standards see Section B

Actions and Uses — Diodo-hydroxyquinoline is used as an antiprotozoan agent for use in amebic dysentery and in the treatment of *Trichomonas hominis* (intestinalis) infections

Dosage — Adults — seven to ten tablets a day for fifteen to twenty days.

B. L. LEMKE & Co. INC.

Yodoxin (*Powder*) 25 Gm 100 Gm. and 454 Gm. bottles and in bulk

Tablets Yodoxin 210 mg

G. D. SEARLE & Co

Tablets Diodoquin 0.21 Gm.

U S trademark 336 484

ODOCHLOROXYQUINOLINE-N. F.—Vioform (CIBA)—5-chloro-7-iodo-8-hydroxyquinoline.—"Contains not less than 38 per cent and not more than 41.5 per cent of I, and not less than 11.4 per cent and not more than 12.2 per cent of Cl."—N. F. The structural formula may be represented as follows:



For description and standards see The National Formulary under Iodochlorohydroxyquinoline and Iodochlorohydroxyquinoline Tablets.

Actions and Uses.—Iodochlorohydroxyquinoline is occasionally used as an almost odorless substitute for iodoform; it is generally employed against trichomonas vaginitis and, internally, against amebiasis. It is used in atopic dermatitis, eczema of the external auditory canal, eczema of the legs, scalp, scrotum and perineum, also in chronic dermatitis, oil dermatitis, acute psoriasis and intertriginous psoriasis.

The diagnosis of amebiasis depends on the observation of motile forms or cysts of *Endameba histolytica* in stool specimens (repeated examinations are often necessary) or their recovery by means of the proctoscope from the intestinal mucosa; positive diagnosis can often be made by the latter procedure when stool examinations are negative, and this is considered to be the more satisfactory as well as the more rapid method of diagnosis in many cases. In view of the frequency of persistent infection in the absence of marked symptoms, adequate therapy includes re-examinations and repetitions of courses of treatment.

Dosage.—Against amebiasis, 0.75 Gm. to 1.0 Gm. daily (in capsules in divided doses of 0.25 Gm. by mouth for 10 days, with repetition of the course after a rest period of a week to ten

cent ointment, lotion or paste.

Caution—Iodochlorohydroxyquinoline used locally stains linen yellow on contact.

CIBA PHARMACEUTICAL PRODUCTS, INC.

Vioform (Powder): Bulk.

Vioform Insufflate: 30 Gm. and 248.8 Gm. bottles containing vioform 25 per cent, boric acid 10 per cent, zinc stearate 20 per cent, lactic acid 2.5 per cent and lactose 42.5 per cent.

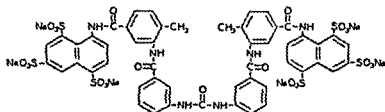
Tablets Vioform: 250 mg

Vioform Vaginal Inserts: Each insert contains vioform 250 mg., lactic acid 25 mg., boric acid 100 mg. and diluent to make 2 Gm.

U. S. patent 641,491 (Jan. 16, 1900; expired) U. S. trademark 92,732

Urea Derivatives

Suramin Sodium is a urea derivative. It is a sodium salt of a tri-sulfonated urea derivative. It is a white, crystalline powder, soluble in water. It is used as a urinary antiseptic and as a diuretic.



For description and standards see the U. S. Pharmacopoeia under Suramin Sodium.

Actions and Uses—Suramin sodium is a trypanosomicide which readily dissolves in sterile water, the solution is neutral in reaction, odorless and almost tasteless. Only freshly made solutions should be used.

safe when properly used, it exerts an irritant action on the kidney, even after comparatively small doses there is frequent

amaurosis and anuria have been noted. In larger doses suramin

It has come into use as a vermifuge in the treatment of hookworm disease. It is reported that usually about 95 per cent of the hookworms are removed by the first dose of carbon tetrachloride and that occasionally all are removed. As a vermifuge it appears to be relatively safe, but serious symptoms and even death have occurred, especially in patients addicted to the use of alcohol. During treatment some of the patients complain of headache. Good results are obtained if the capsules are given with food or milk or three hours after a meal.

capsules may be prepared extemporaneously. Lambert recommends giving the vermicide and a solution of magnesium sulfate together, claiming that this prevents headache. A mild laxative is generally given to constipated patients on the day previous to treatment. To insure complete removal of the hookworms a test dose of oil of chenopodium, 3 cc. (45 minims), may be given a week after the treatment with carbon tetrachloride. A second dose of carbon tetrachloride should not be given within three weeks. Alcohol should not be taken during treatment.

Dosage.—From 2 to 3 cc.; the dose of 3 cc. should not be exceeded. For children 0.13 cc. for each year of age up to 15 years. The capsules should be swallowed immediately, not broken in the mouth. A purgative dose of magnesium sulfate is administered two or three hours after the anthelmintic. A laxative dose of the salt should be administered also on the preceding day.

MERCK & CO., INC.

Carbon Tetrachloride (*Liquid*): Bulk.

TETRACHLOROETHYLENE—U. S. P.—Perchloroethylene.—“Contains not less than 99 per cent and not more than 99.5 per cent of C_2Cl_4 , the remainder consisting of alcohol.” U. S. P. The structural formula may be represented as follows:



For description and standards see the U. S. Pharmacopeia under Tetrachloroethylene and Tetrachloroethylene Capsules.

Actions and Uses.—Observations of many workers have shown that tetrachloroethylene is a useful anthelmintic for the treatment of hookworm infestation. It has been used against other worms with less success, although there is some evidence that it is useful in *Trichuris* infestation. It may be lethal to *Ascaris* but its use in that infestation is not advised because of the danger of causing migration of the worms. It is the consensus of the investigators that tetrachloroethylene is less toxic than carbon tetrachloride (CCl_4) and at least as efficacious as the latter drug. It has a further advantage over carbon tetrachloride

in that it does not raise the guanidine content of the blood, which is important in cases exhibiting a calcium deficiency. Untoward reactions are rare but giddiness, vomiting and drowsiness have been reported in some cases. It is probably better to keep the patient (especially children) in bed during the treatment.

Dosage —From 1 to 3 cc. depending on the age of the patient. Tetrachlorethylene is usually given in soft gelatin capsules but has also been administered to children on a lump of sugar. The gastro intestinal tract should be thoroughly emptied before administering tetrachlorethylene. Fats and alcohol must be avoided because they favor absorption of the drug. A dose of tetrachlorethylene should be followed by a saline cathartic of sodium or magnesium sulfate. One dose frequently suffices but if necessary it may be repeated once after a period of from ten days to two weeks.

Caution —Broken capsules should be discarded; the solution should never be employed if it has been exposed to the air for more than a very brief time because of the possibility of phosgene formation by decomposition.

have been developed of a salt of their pure. Until more is known of their alkaloidal content, curare preparations from various sources should be bioassayed for potency, although the crystalline chloride salt of *d*-tubocurarine may be prescribed on a weight basis. The potency of curare is presently measured by the "head-drop" bioassay in rabbits and is expressed in terms of a unit *d*-tubocurarine only by those dangers. The

anesthetist should have at hand means to establish artificial respiration and to maintain an airway as well as a solution of neostigmine methylsulfate, 1:2,000, for use in 1-cc. or 2-cc. quantities as an antidote in curare overdosage.

PURIFIED CHONDODENDRON TOMENTOSUM EXTRACT—Intocostrin (SQUIBB).—An aqueous preparation containing therapeutically curare. The curare activity is due to an alkaloid, *d*-tubocurarine, total solids in intocostrin excipient and chlorobutanol. The physiologic activity of intocostrin is determined on rabbits: The unit is a potency equivalent to that of 0.15 mg. of a pure or recrystallized *d*-tubocurarine chloride pentahydrate containing the theoretical water content of 11.46 per cent.

For tests and standards, see Section B.

Actions and Uses.—Intocostrin is used for the same purposes as its active principle, *d*-tubocurarine. See the monograph, *d*-Tubocurarine Chloride.

Dosage.—See under *d*-Tubocurarine Chloride.

Preparation.—

Intocostrin prepared from *Chondodendron tomentosum* extract is made by first extracting with alcohol a desiccated curare obtained from a heavy syrup of the bark and stems of *Chondodendron tomentosum*. The extract is concentrated to dryness; a sterile filtered solution to a standard potency of contains sodium chloride 0.45 per cent; sterilized by filtration.

E. R. SQUIBB & SONS

Intocostrin: 5 cc. and 10 cc. vials. Each cc. contains an amount of purified chondodendron tomentosum extract equivalent to 20 units; sodium chloride 0.45 per cent. Preserved with chlorobutanol 0.5 per cent.

U. S. trademark 382,110.

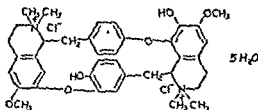
***d*-TUBOCURARINE CHLORIDE.**—The crystalline chloride of a quaternary base alkaloid obtained from the bark and

stems of *Chondodendron tomentosum* and related species *d*-Tubocurarine chloride is assayed biologically by the rabbit cross-over "head-drop" method.

curarine chloride

content of 11.46 g

curarine chloride is assayed as follows



For tests and standards see Section B

Actions and Uses.—*d*-Tubocurarine chloride may be used in conditions in which it is desirable to reduce the tone or contractile power of skeletal muscle. It is useful with light general anesthesia to obtain greater relaxation of the

muscle during metrazol or electro shock therapy and temporarily to lessen the central nervous system activity in severe spastic states.

For anesthesia pre-
pare following doses
either, when only
employed After
to 9 mg (40-60

d-Tubocurarine chloride may be given in a single intravenous injection for the required muscular relaxation, an additional 3 to 4.5 mg (20-30 units) may be given in 3 to 5 minutes and repeated later if necessary. The effect usually appears in about 2 minutes. In overdosage if ventilation is insufficient adequate pulmonary exchange may be maintained by periodic compression of the bag of the anesthetic apparatus when necessary.

In the usual dose is 3 mg weight for greater safety should be used as the drug should be given over a period of not less than 90 seconds. In spastic states where the drug is used to permit training in the voluntary use of muscles it may be administered intramuscularly. The dose is determined by trial, beginning with 3 mg (20 units) intramuscu-

larly for each 40 pounds of body weight and gradually increasing the dose until the amount producing the best results is found. As a diagnostic test for myasthenia gravis, 0.3 mg. (2 units) per 40 pounds of body weight is given intravenously; marked exaggeration of symptoms appears within 2 minutes if myasthenia is present. As soon as a positive reaction is obtained, the curare effect should be antagonized by the intravenous injection of 1 cc. or 2 cc. of neostigmine methylsulfate, 1:2,000 combined with 0.6 mg. of atropine sulfate.

Solutions of *d*-tubocurarine chloride used in conjunction with pentothal sodium intravenous anesthesia may be admixed with a solution of pentothal sodium for simultaneous administration of both agents. Solutions of *d*-tubocurarine chloride are available in concentrations of 3 mg. (20 units) per cubic centimeter and 15 mg. (100 units) per cubic centimeter. The acidity of these solutions causes only momentary precipitation of curare-barbiturate mixtures when added in amounts to avoid undue dilution of the pentothal sodium solution: limit for solution *d*-tubocurarine chloride of 3 mg. (20 units) per cc., is 7.5 units per 25 mg. pentothal sodium in 1 cc.; for solution *d*-tubocurarine chloride of 15 mg. (100 units) per cc., 10 units per 25 mg. pentothal sodium in 1 cc. Optimal results for most operative procedures have been obtained by using 5 units of the higher potency *d*-tubocurarine chloride solution per each 1 cc. of the 2.5 per cent solution of pentothal sodium. This mixture is made up by adding 1 cc. of high potency (100 units per cc.) solution of *d*-tubocurarine chloride to 19 cc. of 2.5 per cent solution of pentothal sodium and, when so made from the high potency *d*-tubocurarine chloride solution, will keep for about 10 days. It is administered in the same manner as pentothal sodium alone, with slow induction, 1 or 2 cc. at a time. The average total dose of the mixture varies from 15 to 20 cc. Other ratios and technics may be worked out to advantage in individual cases. *The high potency solution of d-tubocurarine chloride, 15 mg. (100 units) per cc. should never be injected without dilution because of the*

ABBOTT LABORATORIES

Solution *d*-Tubocurarine Chloride: 3 mg. per cc., 10 cc. vials. Preserved with benzyl alcohol 0.9 per cent.

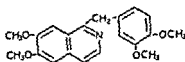
E. R. SQUIBB & SONS

Solution *d*-Tubocurarine Chloride: 3 mg. (20 units) per cc., 10 cc. vials

Solution *d*-Tubocurarine Chloride (High Potency): 15 mg. (100 units) per cc., 1 cc. ampuls.

PAPAVERINE

Papaverine is an alkaloid obtained from opium, belonging to the benzyl isoquinoline group (that is, it is not a morphine derivative). The structural formula may be represented as follows:



For tests and standards, see Section B.

Actions and Uses—Pal found that papaverine relaxes smooth muscle in general, although different organs are affected in a varying degree.

Papaverine is most effective in hypertonic conditions, while it does not interfere materially with the normal movements, for instance, of the intestines. It is also a rather feeble central analgesic and a local anesthetic. Its toxicity is low, and neither

Dosage—The oral and hypodermic single dose is from 30 mg to 80 mg; daily dose to 0.5 Gm. Single doses of even 1 Gm. are said to be nontoxic.

Astringents, Caustics and Sclerosing Agents

...ally for their relatively weak
...nic acid is the most important
...metallic salts possess astringent
...lead, copper and aluminum.
The salts of other metals such as silver and mercury, used primarily for their germicidal effect, are astringent in high dilutions. These are described in the chapter on Local Anti-Infectives. Aluminum compounds used as antacids are described in the chapter on Gastro-intestinal Drugs.

Caustics are agents used locally for chemical cautery or destruction of tissue. The mineral acids and strong alkalis are perhaps the best examples. Of greater therapeutic usefulness, are certain metallic compounds such as silver nitrate and copper sulfate that are astringent in high dilutions, but act as caustics in concentrated form. The term *escharotic*, though synonymous with caustic, is occasionally applied to agents that produce local protein-coagulant effects rather than complete destruction of tissue.

Sclerosing agents are described in this chapter because of their irritant properties, which make them useful for the obliteration of varicose veins. The Council has not accepted agents of this type for other purposes; their use in the treatment of hernia is considered hazardous.

ALUMINUM SALTS

Several of the compounds of aluminum are official, including the ordinary alum or alumer. Aluminum subacetate are used described in The National Solution and Aluminum Subacetate Solution.

The aluminum compounds are used for their astringent action. Since they are but little absorbed, they are relatively nontoxic.

Compounds of aluminum are astringent because of their property of precipitating albumin. The exsiccated alum is more energetic, not only because it contains a larger proportion of alum than the crystalline form, but because it absorbs water

from the tissue at the same time. The acetate is milder than the sulfate, as is usual with metallic salts.

The aluminum compounds are not so astringent as the corresponding lead salts, but they may exert an irritant and even caustic action when used in concentrated solutions or in the form of the exsiccated (burnt) alum. When swallowed in overdoses in such concentrated form they may cause gastritis and diarrhoea. Alum is sometimes used as an emetic.

The aluminum compounds are slightly antiseptic, a property which goes with their astringency. Some of the organic compounds are said to be more actively antiseptic than the inorganic ones.

Several proprietary preparations, consisting of aluminum combined with organic acids, have been introduced with a view to utilizing the astringent and antiseptic properties of their components. Many of these possess no special advantages and have fallen into disuse, or have been largely replaced by others of a more or less similar nature.

COPPER SALTS

CUPRIC CITRATE-U. S. P.—The cupric salt of citric acid and contains not less than 34 per cent and not more than 37 per cent of Cu. [1000000] "U. S. P."

For description and standards see the U S Pharmacopeia under Cupric Citrate and Cupric Citrate Ointment.

Astringent Uses and Dosage.—Copper citrate possesses the astringent and antiseptic properties of other salts of copper somewhat modified by its sparing solubility.

It may be used for the same purposes as and in doses similar to those of other salts of copper. Ointments of 5 to 10 per cent are used locally for the treatment of trachoma.

MALLINCKRODT CHEMICAL WORKS

Copper Chloride (Crystals) Fe²⁺

MANHATTAN FIRE SALES COMPANY, INC.

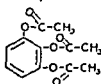
Ophthalmic Ointment Copper Citrate 5%. A sterile ointment containing copper citrate 5 per cent, used for 10 per cent. petrolatum 24 per cent. as base and 1 per cent. preservative.

Ophthalmic Ointment Copper Citrate 10%. A 5 cent seal
must contain copper citrate 10 per cent and fat 10 per cent,
plus at least 2 per cent, without alcohol or preservative.

PYROGALLOL

ACETPYROGALL. — Laccigallol (Hansen) $\times 12$ —
 Transcription of $\frac{1}{2}$ of $\frac{1}{2}$ of $\frac{1}{2}$ of the hydroxylation

of pyrogallol with acetate groups. The structural formula may be represented as follows:



For tests and standards, see Section B.

acute and subacute eczema of children and other skin diseases.

Dosage.—In 5 to 10 per cent ointment, usually with zinc oxide.

BILHUBER-KNOLL CORP.

Lenigallol (Powder): 7.5 Gm. and 30 Gm. bottles.

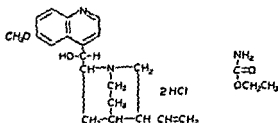
Ointment Lenigallol-Zinc: Contains lenigallol 6 per cent, in zinc oxide ointment-U. S. P.

SCLEROSING AGENTS

and others have been employed as sclerosing agents mainly for the obliteration of varicose veins. Some of the compounds employed for this purpose are combined with local anesthetic agents or possess anesthetic properties themselves. Solutions of dextrose or invert sugar and fatty acid preparations such as sodium morrhuate are less irritating and do not produce necrosis if accidentally injected outside the vein as may occur with more powerful sclerosing substances. The Council has recognized solutions of dextrose (50 per cent), dextrose (25 per cent) and sodium chloride (15 per cent) combined, invert sugar (60 to 75 per cent), sodium morrhuate (5 per cent) combined with local anesthetics, quinine hydrochloride or dihydrochloride (13 per cent) with urethane (6.5 per cent), and sodium ricinoleate

saphenous vein in the presence of incompetency of the valves of that vein; other contraindications include active or recent phlebitis, systemic diseases such as active tuberculosis and hyperthyroidism, acute infections (including the common cold), prolonged recumbency, cardiac decompensation and possibly, pregnancy. In the occasional case where a patchy dermatitis ap-

pears, usually of the legs, and recurs or is exaggerated following succeeding injections of a sclerosing agent it is well to discontinue the use of such agents



For standards see U S Pharmacopeia under Quinine Dihydrochloride and under Urethane.

Actions and Uses—A mixture of quinine dihydrochloride and urethane in aqueous solution is used as a sclerosing agent for injection in the obliterative treatment of varicose veins. The mixture is claimed to have antiseptic qualities. It should not

Dosage—The initial injection should be limited to 0.5 cc. to determine whether idiosyncrasy exists, average amount for in-

DEXTROSE SOLUTION 50%—See monograph on Invert Sugar Solution for actions and uses

INVERT SUGAR SOLUTION—A solution of a mixture of dextrose and levulose obtained by the inversion of sucrose

For tests and standards see Section B

Actions and Uses—Solution of invert sugar is used in the injection treatment of varicose veins. It is claimed that the use of sugar solutions such as solutions of dextrose or of invert sugar have the advantage over solutions of sodium chloride, sodium salicylate or mercuric chloride in that they do not cause severe cramps or sloughing if accidentally injected outside the vein.

Dosage—Depending on the size of the vein, from 5 to 20 cc.

of solution is injected. For young patients whose veins react to solutions of lower concentration, solutions containing from 50 to 60 Gm. of invert sugar in 100 cc. are used; for older patients and varicosities of long standing, a solution containing 75 Gm. of invert sugar in 100 cc. is used.

SODIUM MORRHUATE INJECTION

method . . . not less than 93 per cent and not more than 107 per cent of the labeled amount of sodium morrhuate. A suitable preservative, not to exceed 0.5 per cent, and ethyl or benzyl alcohol, not to exceed 3 per cent, may be added." *U. S. P.*

For standards see the *U. S. Pharmacopeia* under Sodium Morrhuate Injection.

Actions and Uses.—The action of sodium morrhuate is that of a sclerosing agent. It is employed in solution with addition of a local anesthetic for the obliteration of varicose veins. Solutions in concentrations of more than 5 per cent are not recommended, and the possibility of sensitization or idiosyncrasy to sodium morrhuate should be kept in mind to avoid reactions which have been reported in susceptible individuals.

Dosage.—0.5 to 1 cc. of a 5 per cent solution is a relatively safe preliminary test dose and its effects should be studied for 24 hours before proceeding with further injections. An average of 1 cc. is the amount injected at any one site and should not exceed 2 cc. Injection of the saphenous vein at the time of ligation when that procedure is indicated, may require from 5 to 10 cc. of the 5 per cent solution. The number of injections made in one day varies with the patient and should not comprise a total amount of more than 5 cc. To guard against the development of sensitivity it is recommended that the interval of time between the first two injections be not more than five days.

GEORGE A. BREON & COMPANY, INC.

Solution Sodium Morrhuate 5% with Benzyl Alcohol 2%: 5 cc. vials. Each cc. contains sodium morrhuate 50 mg. and benzyl alcohol 20 mg. in aqueous solution.

ENDO PRODUCTS, INC.

Solution Sodium Morrhuate 5% with Benzyl Alcohol 2%: 2 cc. and 5 cc. ampuls and 25 cc. bottle. Each cc. contains sodium morrhuate 50 mg.; and benzyl alcohol 20 mg. in aqueous solution.

LAKESIDE LABORATORIES, INC.

Solution Sodium Morrhuate 5% and Benzyl Alcohol 2%: 30 cc. vials. Each cc. contains 0.05 Gm. of sodium morrhuate and 0.02 Gm. of benzyl alcohol in aqueous solution.

NATIONAL DRUG COMPANY

Solution Sodium Morrhuate 5% with Benzyl Alcohol 2%: 25 cc ampul vials Each cc. contains 50 mg sodium morrhuate and 20 mg benzyl alcohol in aqueous solution.

G D SEARLE & Co

Solution Sodium Morrhuate 5% with Benzyl Alcohol 2%: 5 cc. and 60 cc (serum type vials) Each cc. contains 50 mg sodium morrhuate and 20 mg benzyl alcohol in aqueous solution.

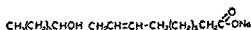
ULMER PHARMACAL COMPANY

Solution Sodium Morrhuate 5% with Benzyl Alcohol 3%: 5 cc. and 20 cc. vials Each cc contains sodium morrhuate 50 mg., benzyl alcohol 30 mg and phenol 5 mg, in aqueous solution.

THE UPJOHN COMPANY

Solution Sodium Morrhuate 5% with Benzyl Alcohol 2% 2 cc. ampuls and 30 cc vials Each cc contains sodium morrhuate 50 mg and benzyl alcohol 20 mg in aqueous solution

SODIUM RICINOLEATE SOLUTION



For tests and standards, see Section B

Actions and Uses—Sodium ricinoleate, like other fatty acid salts is irritant to tissues, and in solution it exerts a useful sclerosing action for the obliteration of varicose veins by injection. Following injection into a varicosity, there is immediate

As with other sclerosing solutions, sodium ricinoleate solution is contraindicated for injection of exposed veins.

Dosage—Sodium ricinoleate for injection of varicose veins is usually employed as a 2 per cent solution. This is considered the concentration of choice for all but the smallest lesions.

that have rarely occurred are mild and of short duration. The

Sodium tetradecyl sulfate is subject to the same general contraindications as for other sclerosing agents. See general statement on Sclerosing Agents.

Dosage.—Sodium tetradecyl sulfate is employed for sclerosing therapy of varicose veins in buffered solutions of 1 per cent.

should be injected at any one occasion. Repeated injections

not more than 1 cc. of the 1 per cent concentration be used as a test dose on the first injection to detect any possible idiosyncrasy. Treatment should not be instituted or continued if alarming reactions occur.

WALLACE & TIERNAN PRODUCTS, INC

Solution Sodium Sotradecol with Benzyl Alcohol 2% :
1, 3 and 5 per cent solution, 20 cc. vials.

U. S. trademark registered.

Autonomic Drugs

The designation "autonomic drugs" is generally applied to those drugs that either mimic or oppose the peripheral effects of nerve impulses of the autonomic (visceral efferent, vegetative, involuntary) nervous system. They have been grouped into four main classes of drugs on the bases of (a) the two anatomical divisions of the autonomic system, namely the sympathetic (thoracolumbar) and the parasympathetic (craniosacral), and (b) the two principal effects, whether stimulating or depressing, upon the given division. Accordingly, the four classes are (1) sympathomimetic, (2) sympatholytic, (3) parasympathomimetic, and (4) parasympatholytic. Since the two divisions are, on the whole, mutually antagonistic, it is seen that drugs of classes (1) and (4) have certain effects in common; thus atropine, which is parasympatholytic, and epinephrine, which is sympathomimetic, both dilate the pupil. Similarly (2) and (3) will sometimes have identical effects.

Certain discrepancies, however, are found in the effects produced by members of these groups and between members of the same group. These discrepancies are partially explained by the known facts of chemical mediation of the nervous impulse. Autonomic fibers that transmit nerve impulses mediated by the epinephrine-like substance or substances called sympathin are called *adrenergic*; most postganglionic sympathetic fibers are of this sort. Autonomic fibers that carry nerve impulses mediated by acetylcholine parasympathetic fiber both sympathetic and ; Acetylcholine has also impulses by "sympathetic" nerves to sweat glands and certain vascular beds, the splanchnic fibers to the adrenal medulla, and even the cerebrospinal motor fibers to skeletal muscle.

The uncertainty that prevails regarding the exact mode and site of action of so-called autonomic drugs makes it difficult to adopt a scheme of classification that takes into account all of their variable effects. One advantage in partially retaining an anatomical viewpoint is that fibers of the sympathetic branch ramify widely through several ganglionic cells so that a diffuse discharge is possible, whereas parasympathetic fibers have terminal ganglia near to the innervated organ so that impulses are more discrete in their effect. Furthermore, cholinesterase causes a rapid destruction of acetylcholine thereby limiting the

effect of cholinergic nerves, whereas sympathin and epinephrine

SYMPATHOMIMETIC AGENTS

[Sympathomimetic agents are broadly defined as those drugs that induce bodily responses which imitate the effects of impulses conveyed by adrenergic postganglionic fibers of the sympathetic nervous system. Most of these agents are aromatic in character, and their action is explained by a substituent on the benzene nucleus. In the case of the molecule is separated into an aromatic and an aliphatic portion.]

also been developed.]

Because of the existing similarities of structure, sympathomimetic agents can be grouped sometimes according to their aromatic portions sometimes according to the aliphatic. Thus, epinephrine and Nephthrine have identical aromatic portions, ephedrine and Propadrine are similarly paired, so are tyramine and Paradrine. Agents such as norepinephrine and phenylephrine have

group attached to the aromatic carbon atom, their differences

arteriolar constrictor effect, fails to exert its characteristic activity if given too frequently (tachyphylaxis) and produces effects on skeletal muscle not shared by epinephrine. The cen-

tral stimulatory effects of ephedrine and amphetamine put these compounds at a disadvantage when their peripheral effects are desired, but at the same time render them useful under other circumstances.

[With cognizance of certain exceptions, sympathomimetic drugs in general produce mydriasis and/or relaxation of the ciliary muscle, decreased tone of bronchioles, stomach, intestine, bladder and ureter, contraction of smooth muscle sphincters, the splenic capsule, and pregnant uterus, constriction of blood vessels other than coronary, inhibition of the secretion of certain glands and increased cardiac rate and output. The actions on the heart, blood vessels and certain smooth muscles are especially prominent and form the basis for their principal therapeutic application. Ventricular arrhythmias, even fibrillation, may follow the use of epinephrine, particularly during surgical anesthesia, so that its use may be dangerous in such circumstances. In patients with medical or surgical shock, it may aggravate the underlying cause; it should not be given in the presence of emphysematous bronchial asthma. Pressor effects

response may be increased or decreased, and in some instances inverted to a depressor action. For instance, Vonedrine pressor action is inverted to a depressor action by the presence of Paredrine, but not by other amines. Epinephrine, while the most potent pressor amine, produces a dilator effect on capillaries that may account for the hypotension seen to follow its transient vasoconstrictor action on the arterioles. Reversal of its constrictor action occurs when preceded by the sympatholytic agents.

Milder side reactions of anxiety, tenseness, restlessness, insomnia, tremor, weakness, palpitation may also interfere with the clinical use of these compounds in certain patients. The claimed advantage of one compound over another in this group is largely dependent upon the purpose for which it is employed, so that what may be considered an undesirable side effect in one instance, becomes a useful "pressant action in another."

AMPHETAMINE — *Amphetamine*

(FRENCH) — Racemic Amp

— Racemic desoxy-nor-epl

racemic mixture having the formula:



For tests and standards, see Section B.

Actions and Uses — Amphetamine produces local effects similar to those of ephedrine. Inhalation of the vapors of amphetamine or its carbon dioxide addition compounds produces shrinking of the nasal mucosa in head colds, sinusitis, vasomotor

rhinitis, hay fever and asthma. Both amphetamine and its carbon dioxide addition compounds (the latter ————) . . .
 posture of ———— . . .

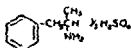
—As an inhalant, one or two inhalations through each nostril at hourly intervals, has been recommended. Continued overdosage should be guarded against, as this has caused restlessness and sleeplessness and also may prolong the local condition being treated. Serious reaction has been reported as a result of overdosage and what may be hypersensitivity to the drug in inhalator form.

SMITH, KLINE & FRENCH LABORATORIES

Benzedrine Inhaler: Each inhaler tube contains, at the time of packing racemic amphetamine 250 mg., menthol 12.5 mg. and aromatics.

U. S. patents 1,921,424 (Aug. 6, 1933, expires 1950), 1,879,001 (Sept. 27, 1932, expires 1949) and 2,013,408 (Sept. 24, 1933, expires 1952).
 U. S. trademarks 272,377 and 350,017.

AMPHETAMINE SULFATE.—**Benzedrine Sulfate** (SMITH, KLINE & FRENCH)—Racemic amphetamine sulfate—[1-Phenyl]-2-aminopropane sulfate. The structural formula of this compound may be represented as follows:



For tests and standards, see Section B.

Actions and Uses.—Amphetamine sulfate has a number of clinical uses. It has been widely employed in the treatment of narcolepsy, in controlling the oculogyric crises and various other manifestations of postencephalitic parkinsonism, as an adjunct in the treatment of alcoholism, and for facilitating roentgenographic studies of the gastrointestinal tract, but its most extensive therapeutic application has been in the treatment of certain depressive conditions, especially those characterized by apathy and psychomotor retardation.

The marked central nervous stimulatory effect of the drug on the central nervous system renders it effective in the symptomatic treatment of many mild psychogenic depressive states, especially those marked by morning tiredness, attending old age, accompanying persistent pain, precipitated by the menopause, characterized by chronic fatigue, masquerading as bodily ailments, following childbirth, prolonged postoperative recovery, associated with chronic organic disease, etc.

Amphetamine sulfate may also be of value, but to a lesser extent, in the symptomatic treatment of the more severe depressions accompanying certain major psychopathic conditions.

There is considerable evidence that, again due to its ameliorative influence on mental depression, it is an adjunct in the treatment of the vicious alcoholic cycle, thus permitting the institution of more fundamental psychotherapeutic measures. In acute alcoholism, with or without accompanying psychosis, the drug may occasionally be useful in combating pathologic intoxication. (In alcoholic psychoses best results are reported where the psychosis is of recent origin.)

In addition, the drug has been reported to be effective in the symptomatic treatment of orthostatic hypotension. It has also been used in spastic colitis, pyloric spasm, and certain other clinical conditions not mentioned above; but such use is not recommended.

Amphetamine sulfate may be useful as a corrective agent in the treatment of the drug, or abandonment of other appropriate measures to correct habits of overeating.

While the drug is useful in the treatment of various depressive states, evidence indicates that it is of little value in altering the course of the underlying psychosis in the major psychopathic conditions. Obviously, in severe depressive psychopathic cases, the patient should be institutionally treated.

variable. In mild psychoses, the drug should be subordinated to efforts directed toward the correction of the underlying causes.

The use of amphetamine sulfate to alleviate sleepiness and fatigue by persons not under medical control is to be condemned. The danger lies in the elimination of the warning signal of fatigue in individuals who are overdoing, the possibility of habit formation on continued use, and the undesirable circulatory effects. Collapse has occurred in some cases when the drug has been so used. Except when administered under the strict supervision of the physician, its use is not recommended for developing a sense of exhilaration, increased energy and capacity for work; nor as a "pick-me-up" following temporary alcoholic overindulgence.

Because of the inherent pharmacological nature of amphetamine, the physician should be fully aware of the possibility that its administration may, in certain instances, produce overstimulation, restlessness, sleeplessness, and gastrointestinal disturbance; and that overdosage may be followed by chills, collapse, and syncope.

Caution should be exercised in the administration of amphetamine sulfate, especially in the presence of anxiety, and the possibility of its producing a state of tension that may be followed by collapse.

the drug, although cases of habit formation have only rarely been reported must be kept in mind

Dosage—Since effective dosage varies considerably with the individual patient and with the condition being treated initial doses should be small (5 mg or less) and should be increased gradually until a definite effect manifests itself. The use of a small test dose is particularly important in the treatment of depressive states. In most cases it is desirable to administer

To depress the appetite in overweight doses of 5 to 10 mg three times daily preferably administered one half to one hour before each meal are usually sufficient. The dosage should be

begin treatment with smaller doses increasing them gradually until optimal results are achieved. (With light sleepers it is best to administer the last daily dose not later than 4 P M)

SMITH KLINE & FRENCH LABORATORIES

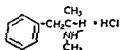
Benzedrine Sulfate (Powder)

Elixir Benzedrine Sulfate 355 cc bottles. Each 5 cc contains racemic amphetamine sulfate 25 mg and alcohol 10 per cent

Tablets Benzedrine Sulfate 5 mg and 10 mg

U S patent 1 879 003 (Sept 27 1932 expires 1949) 1 921 424 (Aug 8 1933 expires 1950) U S trademark 337 407

of methamphetamine hydrochloride the structural formula of methamphetamine hydrochloride may be represented as follows



For tests and standards see Section B

ABBOTT LABORATORIES

Ephedrine (*Powder*): Bulk.

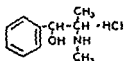
GANE AND INGRAM, INC.

Ephedrine (*Powder*): Bulk.

MERCK & Co., INC.

Ephedrine (*Powder*): Bulk.

EPHEDRINE HYDROCHLORIDE-U. S. P.—"When dried at 100 C. for 3 hours, contains not less than 80.4 per cent and not more than 82.5 per cent of anhydrous ephedrine ($C_{10}H_{15}NO$), corresponding to not less than 98 per cent $C_{10}H_{15}NO \cdot HCl$." U. S. P. The structural formula may be represented as follows:



For description and standards see the U. S. Pharmacopeia under Ephedrine Hydrochloride and The National Formulary under Ephedrine Hydrochloride Tablets.

Actions and Uses.—See general article, Ephedrine.

Dosage.—See general article, Ephedrine.

ABBOTT LABORATORIES

Capsules Ephedrine Hydrochloride: 25 mg.

Solution Ephedrine Hydrochloride: 50 mg. per cc., 1 cc. ampuls.

Solution Ephedrine Hydrochloride 2½% and Procaine Hydrochloride 1%: 2 cc. ampuls.

Solution Ephedrine Hydrochloride 5% and Procaine Hydrochloride 1%: 1 cc. and 2 cc. ampuls.

Syrup Ephedrine Hydrochloride: 0.2195 Gm., 100 cc. and alcohol 12 per cent.

Tablets Ephedrine Hydrochloride: 32.5 mg.

U. S. patent 1,260,289 (March 26, 1918; expired).

AMERICAN PHARMACEUTICAL CO., INC.

Capsules Ephedrine Hydrochloride: 25 mg. and 50 mg.

Solution Ephedrine Hydrochloride 3%: 30 cc. bottle. Preserved with chlorobutanol 0.5 per cent.

GANE AND INGRAM, INC.

Ephedrine Hydrochloride (*Powder*): Bulk.

ELI LILLY AND COMPANY

Pulvules Ephedrine Hydrochloride: 25 mg and 50 mg

Solution Ephedrine Hydrochloride, 3%: Preserved with chlorobutanol 0.5 per cent.

Syrup Ephedrine Hydrochloride: 0.22 Gm, 100 cc. and alcohol 12 per cent. Flavored with vanillin, benzaldehyde and tolu, and tinted with amaranth

MERCK & Co., Inc.

Ephedrine Hydrochloride (Powder): Bulk.

PARKE, DAVIS & COMPANY

Capsules Ephedrine Hydrochloride: 25 mg and 50 mg.

PITMAN-MOORE Co., DIVISION OF ALLIED LABORATORIES, INC.

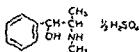
Capsules Ephedrine Hydrochloride: 24 mg.

WARREN-TEED PRODUCTS COMPANY

Capsules Ephedrine Hydrochloride: 25 mg.

EPHEDRINE SULFATE-U. S. P.—"When dried at 100 C. for 3 hours, contains not less than 75.5 per cent and more than 77.3 per cent of $\text{C}_{10}\text{H}_{15}\text{NO} \cdot \text{H}_2\text{SO}_4$ corresponding to

SO_4 U. S. P. I
follows:



For description and standards see the U. S. Pharmacopeia under Ephedrine Sulfate and Ephedrine Sulfate Tablets and the National Formulary under Ephedrine Sulfate Ampuls, Ephedrine Sulfate Capsules, Ephedrine Sulfate Jelly, Ephedrine Sulfate Solution and Ephedrine Sulfate Syrup

Actions and Uses—See general article, Ephedrine.

Dosage—See general article, Ephedrine

ABBOTT LABORATORIES

Capsules Ephedrine Sulfate 25 mg and 50 mg

Solution Ephedrine Sulfate, 25 mg and 50 mg., 1 cc. ampuls

AMERICAN PHARMACEUTICAL Co., Inc.

Solution Ephedrine Sulfate, 3%: 30 cc. bottle Preserved with chlorobutanol 0.5 per cent

Capsules Ephedrine Sulfate: 25 mg and 50 mg

BURROUGHS WELLCOME & Co., Inc.

Solution Ephedrine Sulfate 50 mg., 1 cc. ampuls.

under Epinephrine, Epinephrine Inhalation, Epinephrine Injection and Epinephrine Solution.

Actions and Uses.—Epinephrine acts peripherally on a variety of structures by stimulating directly the effector cells innervated by the sympathetic nerves. Its most important actions consist of a constriction of the blood vessels of the skin, dilatation of blood vessels of the voluntary and heart muscles, and stimulation of the heart with an increase in cardiac output, a rise in systolic arterial pressure and a widening of pulse pressure. Relaxation of the bronchial muscles and also glycosuria follow intramuscular or hypodermic injection. Moderate doses, when given by mouth, have practically no action. However, in hypersensitive patients, such as those with thyrotoxicosis, the administration of epinephrine by mouth may occasionally produce typical effects. The effect of a single intravenous dose is fleeting.

tion; because of the marked increase in vital capacity produced by the drug it is most valuable for treating a severe acute attack of asthma. If, however, asthmatic paroxysms are frequent it is generally advisable to use ephedrine with or in place of epinephrine. By parenteral injection epinephrine is used to treat serum sickness, anaphylaxis, the nitritoid reaction following arsphenamine therapy, urticaria, and angioneurotic edema. Intravenous injections are sometimes effective in anesthesia accidents (care being taken not to give an overdose) and in emergency cardiac failure as in drowning and electrocuting. It is of little or no value in Addison's disease. Epinephrine in the form of a 2 per cent solution of a salt of epinephrine has been used locally in the treatment of glaucoma with apparently favorable results in certain cases, while in other cases it appears to be ineffective.

Untoward reactions which frequently occur following administration of epinephrine are: headache, anxiety, restlessness, insomnia, tremor, palpitation, tachycardia, hypertension, and angina pectoris and hyperthyroidism. The drug should not be used in shock.

The vasoconstrictor action of epinephrine is used to prolong the anesthetic effect of local anesthetics by retarding the circulation in the injected area thus hindering the removal of the anesthetic agent by too rapid absorption into the blood stream. In the same manner it is believed to lessen the toxicity of the local anesthetics by retarding their absorption into the general circulation.

Dilute aqueous solutions rapidly lose their strength, the deterioration being accompanied by a reddish or brownish discoloration.

To avoid any risk of creating a local anæsthetic which may lead to a local anæsthetic solution at one time should never be greater than 1 mg (1 cc.)

Dosage—Hypodermically or intramuscularly from 0.06 to 1 cc. of a 1 in 1,000 solution of epinephrine hydrochloride. Locally, it is used in solution varying in strength from 1 in 15,000 to 1 in 1,000. Epinephrine is also used in solution, in ointment for application to mucous membranes, such as the eye or the nose, where a slower but more lasting action is desired, and in suppositories.

THE ARMOUR LABORATORIES

Suprarenalin (Crystals): 63 mg. vials

U. S. patent 839,220 (Aug. 21, 1906, expired)

PARKE, DAVIS & COMPANY

Adrenalin (Crystals) Bulk.

Inhalant Adrenalin with Chloretone 3%. A glycerin solution containing 1 part of epinephrine (as epinephrine hydrochloride) in 1,000, 3 per cent of chloretone, 15 per cent of alcohol, and aromatics.

Ointment Adrenalin. Contains epinephrine hydrochloride equivalent to one part of epinephrine in 1,000 parts of oleaginous ointment base.

Solution Adrenalin Chloride 1:2,600. 1 cc. ampuls containing sterile solution 1 part of epinephrine hydrochloride in 2,600 parts of isotonic solution of sodium chloride, with not more than 0.1 per cent of sodium bisulfite as a preservative.

Solution Adrenalin Chloride 1:10,000. 1 cc. ampuls containing sterile solution 1 part of epinephrine hydrochloride in 10,000 parts isotonic solution of sodium chloride with not more than 0.1 per cent of sodium bisulfite as a preservative.

Suppositories Adrenalin. One part of epinephrine (as epinephrine hydrochloride) to 1,000 parts of oil of theobroma.

Tablets Adrenalin. 0.33 mg. Each contains 0.33 mg. epinephrine borate, yielding a 1 in 1,000 solution when dissolved in $\frac{1}{2}$ cc. water. Each tablet contains not more than 0.33 mg. of sodium bisulfite.

U. S. patents 730,175, 730,176, 730,196, 730,197, 730,198 (June 2, 1903, expired), 733,177 (Feb. 23, 1904, expired) U. S. trademark 33,934

THE UPJOHN COMPANY

Solution Epinephrine Hydrochloride 1:1,000: 1 cc.
 ampuls and 30 cc. bottles for topical use. Preserved with chloro-
 butanol 0.5 per cent.

U. S. STANDARD PRODUCTS CO.

Solution Epinephrine Hydrochloride 1:1,000: 1 cc.
 ampuls and 30 cc. bottles for topical use. Preserved with chloro-
 butanol 0.5 per cent.

WARREN-TEED PRODUCTS COMPANY

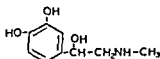
Solution of Epinephrine Hydrochloride 1:1,000: 30 cc.
 vials. Contains epinephrine hydrochloride 0.1 per cent in isotonic
 solution of sodium chloride. Preserved with sodium bisulfite 0.1
 per cent and chlorobutanol 0.5 per cent.

WILSON LABORATORIES

Solution Epinephrine Hydrochloride 1:1,000: 30 cc.
 bottles and vials, for topical use in isotonic solution of sodium
 chloride. Preserved with chlorobutanol 0.5 per cent and sulfurous
 acid 0.06 per cent.

EPINEPHRINE IN OIL SUSPENSION, 1:500.—

Adrenalin in Oil, 1:500 (PARKE, DAVIS).—Suspension of
 epinephrine base 1:500. A 0.2 per cent suspension, containing
 1 part of epinephrine U. S. P. to 500 parts of vegetable oil.
 The structural formula of epinephrine may be represented as
 follows:



For tests and standards, see Section B.

Actions and Uses—Injections of solutions of epinephrine salts
 (1:1,000) are known to provide prompt but transient relief in
 the treatment of severe attacks of bronchial asthma by relaxa-
 tion of the bronchial muscles. Recent evidence indicates that
 injections of vegetable oil suspensions of epinephrine base
 (1:500) delay and prolong the action of the drug and thus
 provide more sustained symptomatic relief in this condition as
 well as in certain cases of hay fever, urticaria, angioneurotic
 edema and serum sickness. The usual contraindications to
 epinephrine must be kept in mind. The preparation should not
 be given to the aged or to patients with hypertension because of
 its prolonged pressor effect. The long disagreeable side
 overdosage in less toxic

irritation by the oil especially when injected subcutaneously, have also been reported. For this reason it is recommended that it be administered intramuscularly and that particular attention be paid to the possibility of scar formation (fibrosis) at the sites of injection. Reactions from the epinephrine itself may be partially avoided by adequate resuspension (shaking) of any precipitate in the oil, the use of a dry syringe and needle and precautions to prevent injecting directly into the blood stream by withdrawal of the syringe plunger to determine the location of the needle point in relation to a vessel before each injection and caution in the selection of the initial dose. The use of a small caliber needle to minimize trauma to blood vessels is also recommended. Intravenous injection is of course contraindicated.

Dosage—Intramuscularly from 0.2 cc. to 1.5 cc. (0.4 mg to 30 mg epinephrine base) administered every eight to sixteen hours. The initial dose for adults should never exceed 0.5 cc. (1 mg epinephrine base) and caution is necessary when subsequent doses larger than 1.0 cc. are employed because of the small amount of epinephrine introduced (1 cc. of 2 mg per cc. contains 2 mg of epinephrine base). For prolonged action Doses

ABBOTT LABORATORIES

Suspension Epinephrine in Oil 1 500 2 mg per cc in 1 cc. purified peanut oil, 1 cc ampuls. A suspension of 2 mg of epinephrine.

ENDO PRODUCTS, INC.

Suspension Epinephrine in Oil 1 500 2 mg per cc in 1 cc. peanut oil 1 cc ampuls. A suspension of 2 mg of epinephrine.

LAKESIDE LABORATORIES INC.

Suspension Epinephrine in Oil 1 500 2 mg per cc in 1 cc sesame oil 1 cc ampuls. A suspension of 2 mg powdered epinephrine crystals. Preserved with chlorobutanol 0.5 per cent.

PARKE, DAVIS & COMPANY

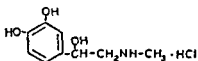
Suspension Adrenalin in Oil 1 500 2 mg per cc. in 1 cc peanut oil 1 cc ampuls. A suspension of 2 mg of crystalline epinephrine.

U S patents 730,175 730,176 730,196 730,197, 730,198 (June 3 1903 exp red) 733,177 (Feb 23 1904 exp red) U S trademark 53,934

SMITH DORSEY COMPANY

Suspension Epinephrine in Oil 1 500 2 mg per cc. in 1 cc peanut oil 1 cc ampuls. A suspension of 2 mg of crystalline epinephrine.

EPINEPHRINE HYDROCHLORIDE SOLUTION, 1:100.—Adrenalin Chloride, 1:100 (PARKE, DAVIS).—Suprarenalin Solution, 1:100 (ARMOUR).—A solution containing 1 part of epinephrine hydrochloride in 100 parts of isotonic solution of sodium chloride. The structural formula of epinephrine hydrochloride may be represented as follows:



Actions and Uses—Injections of solutions of epinephrine (1:1,000) are known to be useful in the treatment of severe attacks of bronchial asthma. Recent evidence indicates that the oral inhalation of solution of epinephrine ten times stronger than those used by hypodermic injection gives relief in acute attacks of bronchial asthma when other measures fail. The physician should familiarize himself with the procedure before employing it in the treatment of his patients. It is absolutely essential that such treatment be instituted under the supervision of the physician and the patient warned of the dangers of using a solution of such strength carelessly. It is also necessary that the atomizer or nebulizer which is used in the administration of such solutions produce a fine mistlike spray free from minute droplets. Every precaution must be taken to avoid confusion between this solution (1:100) and the official 1:1,000 epinephrine solution, since the 1:100 solution is not suitable for hypodermic use and should never be employed in that manner.

Dosage.—A definite dosage cannot be stated for the use of this preparation. It is obviously essential that the amounts used not exceed the minimal amount which will give effective relief. It is best to start with a single compression of the bulb of the atomizer or nebulizer until it is determined what dosage is adequate and safe. Its use should not be repeated until several minutes have passed so that the full effect of the inhalation can be observed before additional amounts are used.

THE ARMOUR LABORATORIES

Solution Suprarenalin 1:100: A solution of epinephrine hydrochloride 1.0 per cent. Preserved with chlorobutanol 0.5 per cent and sodium bisulfite 0.1 per cent.

U. S. patent 829,220 (Aug. 21, 1906, expired).

BRISTOL LABORATORIES, INC.

1:100: 10 mg. per vials. Preserved mg.

BURROUGHS WELLCOME & Co, INC.

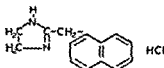
Solution of Epinephrine Hydrochloride 1:100: Each cc. contains epinephrine hydrochloride 1 per cent in isotonic solu-

tion of sodium chloride, 5 cc. vials Preserved with chlorobutanol 0.5 per cent and sodium bisulfite 0.3 per cent

PARKE, DAVIS & COMPANY

Solution of Adrenalin Chloride 1:100: A solution of epinephrine hydrochloride 10 per cent, 5 cc. vials Preserved with chlorobutanol 0.5 per cent and sodium bisulfite 0.1 per cent.

U. S. patents 730,175; 730,176; 730,196; 730,197; 730,198 (June 2, 1903, expired); 753,177 (Feb. 23, 1904, expired). U. S. trademark 51,934.



For tests and standards, see Section B

and acute and chronic administration. Care should be exercised, however, when vasoconstrictors are used for prolonged medication; naphazoline hydrochloride is no exception, although the rebound congestion of the mucosa which it may cause can be alleviated within a few days simply by discontinuing all nasal medication. Those who respond with rebound congestion may tolerate solutions weaker than the commonly used concentrations. The site of action is probably the effector cells innervated by the sympathetic nerves, a property assumed for epinephrine, although further work is needed to clarify this point. So far, there have been no reports proving that sufficient drug is absorbed following local application to increase the blood pressure, although this possibility should not be forgotten.

Dosage—A 0.05 per cent solution of the drug may develop sensitivity of several hours.

For children, the 0.05 per cent solution is suggested.

CIBA PHARMACEUTICAL PRODUCTS, INC.

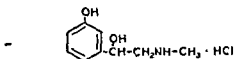
Nasal Jelly Privine Hydrochloride 0.05%: 20 Gm. tubes. Each 1 Gm. contains naphazoline hydrochloride 0.5 mg. in a buffered water soluble base containing glycerin, tragacanth and aromatics. Preserved with sodium ethylmercurithiosalicylate 0.01 mg.

Solution Privine Hydrochloride 0.1% (For Adults Only): 30 cc. and 480 cc. bottles. Each 100 cc. contains naphazoline hydrochloride 100 mg., exsiccated sodium phosphate 0.258 Gm., sodium chloride 0.324 Gm., potassium chloride 0.223 Gm. and potassium biphosphate 0.742 Gm. Preserved with sodium ethylmercurithiosalicylate 1:100,000.

Solution Privine Hydrochloride 0.05% (For Children): 30 cc. and 480 cc. bottles. Each 100 cc. contains naphazoline hydrochloride 50 mg., exsiccated sodium phosphate 0.258 Gm., sodium chloride 0.331 Gm., potassium chloride 0.223 Gm. and potassium biphosphate 0.742 Gm. Preserved with sodium ethylmercurithiosalicylate 1:100,000.

U S patent 2,161,938 U. S. trademark 398,004

PHENYLEPHRINE HYDROCHLORIDE. — *Neo-Synephrine Hydrochloride* (WINTHROP-STEARNs). — laevo- α -hydroxy- β -methylamino-3-hydroxyethylbenzene hydrochloride. 1-(*m*-hydroxyphenyl)-2-methylaminoethanol hydrochloride. — The hydrochloride of the laevo isomer of a synthetically prepared derivative of phenylethylamine having the formula shown below.



For tests and standards, see Section B.

Actions and Uses.—Phenylephrine hydrochloride is a vasoconstrictor and is active as a vasopressor when administered orally. It is more powerful in vasoconstrictive ability than synephrine tartrate, and possesses a relatively low toxicity. Applied to mucous membranes it causes contraction of the small blood vessels, thus reducing swelling and congestion of such membranes. Phenylephrine hydrochloride may be useful in the symptomatic treatment of the disorders of the motor rhinitis as for injection, in retard the systemic absorption of the anesthetic and to prolong its action by local vasoconstriction. It may be injected alone for vasopressor effects as a preliminary or supportive measure

to combat acute hypotension in spinal anesthesia. It may be similarly employed in other acute hypotensive states due to peripheral circulatory collapse (vasomotor failure), but the present evidence does not justify its use in true shock where vasomotor activity is unimpaired and the fall in blood pressure is mainly the result of the loss in circulating blood volume. Its value as a cardiac stimulant is at present conjectural. It may also be used as a mydriatic in the eye preliminary to fundoscopic examination and in conjunction with cycloplegics in the detection of refractive error.

Dosage—For topical application to the nasal mucous membrane the 0.25 per cent solution is ordinarily used.

For the eye, one or two drops of the 1 per cent solution or emulsion or the 2½ per cent ophthalmic solution, as a temporary mydriatic.

The 10 per cent emulsion may be used as a decongestant for the nose.

Because of the irritation produced by the 10 per cent solution or emulsion. The ½ per cent, the 2½ per cent and the 10 per cent ophthalmic solutions contain, in addition to the active ingredient, 0.5 per cent of Aerosol OT 100.

Phenylephrine hydrochloride solutions, it may be used as a decongestant for the nose.

When used as a decongestant.

When used as a decongestant.

Phenylephrine hydrochloride 1%: 15 cc. per cent, sodium benzoate

in a mineral oil and water emulsion containing acacia. Preserved with chlorobutanol 0.5 per cent.

Emulsion Neo Synephrine Hydrochloride 10%: 3 cc. bottle. Phenylephrine hydrochloride 10 per cent, sodium benzoate 0.4 per cent in a mineral oil and water emulsion containing acacia. Preserved with sodium bisulfite 0.1 per cent, ascorbic acid 1 per cent and chlorobutanol 0.5 per cent.

Jelly Neo-Synephrine Hydrochloride 0.5%: Phenylephrine hydrochloride, 0.5 per cent and sodium chloride 0.5 per cent, incorporated in a jelly-like bland base composed of tragacanth, chondrus, glycerin and water. Sodium benzoate 0.45 per cent is present as preservative. The product is supplied in collapsible tube containers.

Solution Neo-Synephrine Hydrochloride $\frac{1}{8}\%$: 15 cc. bottles. Phenylephrine hydrochloride $\frac{1}{8}$ per cent, sodium chloride 1.1 per cent, boric acid 1.5 per cent Aerosol OT 100, 0.001 per cent, boric acid 1.5 per cent Aerosol OT 100, 0.001 per cent, sodium citrate 0.441 per cent. Preserved with chlorobutanol 0.4 per cent and sodium bisulfite 0.1 per cent in an aqueous solution.

Solution Neo-Synephrine Hydrochloride 0.25%: 29.5 cc. and 473 cc. bottles.

Solution Neo-Synephrine Hydrochloride 1%: 29.5 cc., 118.3 cc. and 473 cc. bottles. Phenylephrine hydrochloride 1 per cent, sodium benzoate 0.1 per cent, and sodium chloride 0.5 per cent and sodium bisulfite 0.1 per cent in distilled water.

Solution Neo-Synephrine Hydrochloride 1%: (for Parenteral Use): 5 cc. vial and six 1 cc. ampuls. A sterile solution of phenylephrine hydrochloride 1 per cent, sodium bisulfite 0.1 per cent and sodium chloride 0.6 per cent, in distilled water.

Solution Neo-Synephrine Hydrochloride $2\frac{1}{2}\%$: 15 cc. bottles. Phenylephrine hydrochloride $2\frac{1}{2}$ per cent, sodium citrate 0.441 per cent, Aerosol, OT 100, 0.001 per cent boric acid 0.44 per cent. Preserved with chlorobutanol 0.4 per cent and sodium bisulfite 0.1 per cent in an aqueous solution.

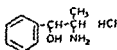
Solution Neo-Synephrine Hydrochloride 10%: 4 cc. bottles. Phenylephrine hydrochloride 10 per cent, sodium citrate 0.441 per cent, Aerosol, OT 100, 0.001 per cent boric acid 0.44 per cent and sodium bisulfite 0.1 per cent in an aqueous solution.

Solution Neo-Synephrine 0.25% in Isotonic Solution of Three Chlorides (with Aromatics): 29.5 cc. and 473 cc. bottles. Phenylephrine hydrochloride 0.25 per cent, sodium sulfite not more than 0.11 per cent, with camphor, menthol and eucalyptol in isotonic solution of three chlorides.

U. S. patent 1,932,347 and 1,954,389 (April 10, 1934; expires April 10, 1951). U. S. trademark 90,142

HYDROCHLORIDE
(NAME).—The hydrochloride of propadrine, differing from

ephedrine by having no methyl group on the amino nitrogen. The structural formula may be represented as follows.



For tests and standards, see Section B

Actions and Uses—Phenylpropanolamine hydrochloride acts as a vasoconstrictor. When used locally in the form of a

prolonged than that of ephedrine. It is also claimed that the anxiety complex is not so apt to ensue with phenylpropanolamine hydrochloride as with ephedrine.

Dosage—As a spray or instillation, 1 per cent aqueous solution or application of 0.66 per cent jelly locally, orally, as a 24 mg capsule every two to four hours as indicated. Although no toxic effects have been noted, continued overdosage should be avoided as with other vasoconstrictors.

SHARP & DOHME, INC.

Elixir Propadrine Hydrochloride. Each 30 cc. contains phenylpropanolamine hydrochloride 0.13 Gm. in a menstruum composed of alcohol 16 per cent glycerin, sucrose and water, flavored with oil sweet orange fluidextract licorice and oil ceylon cinnamon, and colored with carmoisin (certified) and caramel.

Capsules Propadrine Hydrochloride: 24 mg and 48 mg

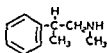
Nasal Jelly Propadrine Hydrochloride 0.66% One-half ounce nasal tip collapsible tubes containing 0.66 per cent phenylpropanolamine hydrochloride with sodium chloride, menthol, thymol and oil of lavender in a water soluble base. Preserved with chlorobutanol 0.5 per cent.

Solution Propadrine Hydrochloride 1% An aqueous solution containing 1 per cent phenylpropanolamine hydrochloride and made isotonic by the addition of 0.58 per cent sodium chloride. Preserved with chlorobutanol 0.5 per cent.

Solution Propadrine Hydrochloride 3% An aqueous solution containing 3 per cent phenylpropanolamine hydrochloride. Preserved with chlorobutanol 0.5 per cent.

U. S. patent 1,937,091 (Jan. 22, 1935, expires 1952). Propadrine is a U. S. registered trademark, but the firm disclaims any proprietary rights to the name.

PHENYLPROPYLMETHYL AMINE — Vonedrine (MERRELL). — Racemic β -phenyl-*n*-propylmethylamine. — Racemic 1-methylamino-2-phenylpropane. — β -Methylaminocumene. — 1-Methylamino-2-methyl-2-phenylethane. — The *N*-monomethyl derivative of β -phenyl-*n*-propylamine. The structural formula may be represented as follows:



For tests and standards, see Section B.

Actions and Uses.—Phenylpropylmethyl amine base is volatile and therefore effective by inhalation, serving as a nasal vasoconstrictor. Its use is claimed to produce little or no evidence of irritation, local tissue reactions or central nervous system and cardiovascular stimulation.

Dosage.—In using the phenylpropylmethyl amine inhaler one long inhalation through each nostril is usually sufficient. This may be repeated as needed, although until more information is available in the entire field of sympathomimetic amine compounds, especially those used locally as nasal vasoconstrictors, the usual care concerning such compounds should be exercised.

THE WM. S. MERRELL COMPANY

Inhaler Vonedrine: Each inhaler contains at the time of manufacture not less than 0.250 Gm. of beta-phenyl-*N*-propylmethylamine and aromatics.

U S patent 2,298,630, U S trademark 406,970

RACEPHEDRINE. — Racemic Ephedrine. — Racemic-1-Phenyl-2-methylaminopropanol-1. The structural formula may be represented as follows:



For tests and standards, see Section B.

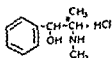
Actions and Uses—The same as those of 1-ephedrine.

Dosage.—From 30 to 50 mg.

GANE'S CHEMICAL WORKS, INC.

Racephedrine (Crystals): Bulk.

RACEPHEDRINE HYDROCHLORIDE. — Racemic Ephedrine Hydrochloride — Racemic-1-Phenyl-2-methylamino-propanol-1 hydrochloride. The structural formula may be represented as follows:



For tests and standards, see Section B.

Actions and Uses—The same as those of l-ephedrine hydrochloride.

Dosage.—From 30 to 50 mg

GANE'S CHEMICAL WORKS, INC

Racephedrine Hydrochloride (*Crystals*): Bulk.

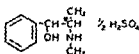
THE UPJOHN COMPANY

Racephedrine Hydrochloride (*Powder*): 120 Gm bottles.

Capsules Racephedrine Hydrochloride: 25 mg

Solution Racephedrine Hydrochloride 1% in Ringer's Solution: Contains in each 100 cc. racephedrine hydrochloride, 1 Gm, chlorobutanol, 0.5 Gm, sodium chloride, 0.86 Gm, potassium chloride, 30 mg, and calcium chloride, 33 mg dissolved in distilled water

phedrine Sul-
sulfate The



For tests and standards, see Section B

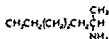
Actions and Uses—The same as those of l-ephedrine sulfate.

Dosage—From 30 to 50 mg

GANE'S CHEMICAL WORKS, INC.

Racephedrine Sulfate (*Crystals*): Bulk.

TUAMINE-Lilly.—Racemic 2-aminoheptane.—The structural formula of 2-aminoheptane is:



For tests and standards, see Section B

Actions and Uses—This compound produces vasoconstrictive action and is a member of the group of compounds known as sympathomimetic amines. Inhalation of the vapors provides an

structure as does acetylcholine. Various choline derivatives have been synthesized that are sufficiently stable in the presence of parasympathetic action. Metha-

The typical parasympathetic effects, in addition to cardiac inhibition, are vasodilation in certain areas, miosis, and increased gastro-intestinal motion and secretion.

A recent addition to the group of parasympathomimetic drugs is di-isopropylfluorophosphate, which surpasses physostigmine and neostigmine in exerting a powerful inhibition on cholinesterase. It produces, for instance, a prolonged miosis, which may prove helpful in the treatment of glaucoma.

Acetyl-beta-methylcholine

... derivative with suffi-
... ay be employed in
... isympathetic stimu-
... "parasympathetic"
... the latter's "nico-
... t the sinoauricular
node, auricular musculature and auriculoventricular node and

the ... physiological antagonist to epineph-
rin ... hysostig-
mi ... nesterase
bu ...

log ... and subcu-
taneously its actions appear to be more prolonged than those of acetylcholine, although the effect on the heart rate and blood pressure persists for only a few minutes. Its intravenous injection is dangerous.

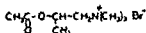
Crystalline water-soluble salts of the base, acetyl-beta-methylcholine, are employed to produce the effects of the drug. The salts are more or less hygroscopic, and if this tendency is extreme, as in the case of the chloride, the crystals must be protected from atmospheric moisture until placed in solution. Acetyl-beta-methylcholine chloride is therefore not suitable for oral administration in crystalline form but should be given in solution. The entire contents of containers of this salt should be put into solution immediately when these are once opened. Solutions of acetyl-beta-methylcholine chloride are fairly stable and will keep for at least two or three weeks. They are relatively stable to heat and may be refrigerated to delay mold growth

The application of aqueous solutions of acetyl-beta-methylcholine chloride by the method of ion transfer (iontophoresis) to introduce this salt into the tissues by means of direct (galvanic) current is recognized as the best means to obtain the local

serious or dangerous nature.

The following precautions should be observed in the administration of the drug. (1) Never administer intravenously because of the danger of cardiac arrest, (2) consider bronchial

METHACHOLINE BROMIDE — Mecholyl Bromide (MERCK) — Acetyl-beta-methylcholine bromide — Trimethyl-beta-acetoxy propyl-ammonium bromide — The acetyl ester of beta-methylcholine bromide. The structural formula may be represented as follows.



For tests and standards, see Section B

methacholine bromide other than by oral administration are not permissible and it should be kept in mind that for those skilled in the technic of ion transfer (iontophoresis) the local application of the chloride by this method is generally to be preferred in the treatment of chronic ulcers, scleroderma, Raynaud's disease and other vasospastic conditions of the extremities, except possibly the management of vascular spasm from exposure to moderate cold.

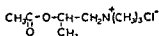
scleroderma and Raynaud's disease the larger doses are required. With patients in whom a total daily dose of 2 Gm. (10 tablets) of the drug is not effective, the oral method of treatment should be abandoned in favor of the use of methacholine chloride by subcutaneous administration or local application by the method of ion transfer (iontophoresis).

MERCK & Co, Inc.

Tablets Mecholyl Bromide: 0.2 Gm.

U. S. patent 2,040,146 (May 12, 1936; expires 1953). U. S. trademark 318,783.

METHACHOLINE CHLORIDE-U. S. P.—Mecholyl Chloride
methyl-bet:
ester of
formula:



For description and standards see the U. S. Pharmacopeia under Methacholine Chloride, Methacholine Chloride Capsules and Methacholine Chloride Injection.

Actions and Uses.—Methacholine chloride is useful in the treatment of selected cases of paroxysmal auricular tachycardia not responding to the usual therapeutic measures, by subcutaneous injection only, in the palliative local treatment of chronic

chronic ulcers,
astatic conditions
of ion transfer
(iontophoresis) but also by oral or subcutaneous administration when the former cannot be employed. For the prevention of attacks of paroxysmal auricular tachycardia the drug is inferior to quinidine. It is of no apparent value in the treatment of of
possibility
resumption
for the use
abdominal
functional

tension are not warranted on the basis of existing clinical evidence. (Also see monograph, Methacholine Bromide.)

Dosage—Considerable variation in the oral dosage requirements is to be expected because methacholine chloride is to some extent destroyed by the gastric juice. The therapeutically effective oral dose usually ranges from 0.2 to 0.5 Gm. two or three

times a day, administered by dissolving in a little water which may be added to milk to disguise the bitter taste. In overcoming vascular spasm due to moderate exposure to cold, oral doses of from 50 mg. to 0.1 Gm. have been found to be effective. In Raynaud's disease, scleroderma and ulcers the effective oral dose may be somewhat higher.

The subcutaneous dose should be limited to 10 mg. on the first injection to test the patient's tolerance. If well tolerated, the dose may be cautiously increased up to 25 mg. This dose is usually adequate for injection when this method of adminis-

tion (1.500 to 1.200) solution of the drug in distilled water. The solution is applied by moistening the positive electrode fabric which is placed over or near the part to be treated. The strength and duration of the galvanic current regulates the dosage and should always be applied gradually and within the point of comfortable tolerance by the patient. The patient should be instructed to report any sensation of excessive heat or burning. If this occurs the treatment should be stopped and an inspection made to determine if an electrode is improperly placed. The initial treatment should not exceed 5 to 10 milliamperes for thirty minutes. Subsequent treatments usually require from 25 to 30 milliamperes applied for twenty to thirty minutes. Each treatment should be restricted to a limited area such as one hand or one joint when several parts are involved. Three or four days is considered the most satisfactory interval between treatments. The number of treatments necessary to obtain results varies with the patient and with the type of lesion. In Raynaud's disease and scleroderma, ten or more treatments may be necessary to secure improvement. In chronic rheumatoid arthritis the treatments may be reduced to intervals of a week after the first four to six treatments, in varicose indolent and gangrenous ulcers treatments may be given daily at the start

and the patient should remain quiet and be kept warm before being permitted to resume protected activity.

Idiosyncrasy to methacholine chloride may result in difficulty in breathing. If this is noted the treatment should be stopped and the patient raised to a sitting position. If untoward symptoms

do not subside, atropine sulfate should be given hypodermically at once.

MERCK & Co., Inc.

Mecholyl Chloride (Powder): 1 Gm. and 10 Gm. bottles for the preparation of solutions for oral administration and for ion transfer (iontophoresis).

Mecholyl Chloride (Powder): 25 mg. ampul for the preparation of solutions for subcutaneous injection.

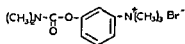
U. S. patent 2,040,146 (May 12, 1936; expires 1953). U. S. trademark 318,783.

Neostigmine

Experimental work indicates that the neostigmine component is more stable than physostigmine and which it has the advantage of being more stable. Apparently, it is as effective in stimulating intestinal peristalsis and gastric activity. There is less toxicity produced by toxic doses of neostigmine than those produced by physostigmine or its salts. This latter fact becomes especially important when it is considered that neostigmine preparations are used by subcutaneous and intramuscular injection, since the neostigmine component is from four to six times as toxic as physostigmine when injected subcutaneously in the rabbit. Atropine is the antidote to neostigmine. Neostigmine preparations are used for the prevention of atony of the intestinal and bladder musculature, and for the symptomatic control of myasthenia gravis. Their use for the prevention and treatment of intestinal and bladder atony is based on activity as a vagotonic agent; their anti-curare-like action is the basis of application in the symptomatic treatment of myasthenia gravis. The drug is also credited with mild laxative action but its use solely for that purpose is not advisable.

Neostigmine is available only in the form of its salts.

U. S. P. The structural formula may be represented as follows:



For description and standards see the U. S. Pharmacopeia under Neostigmine Bromide and Neostigmine Bromide Tablets.

Actions and Uses—See general statement on Neostigmine.

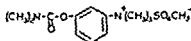
Neostigmine bromide is used for the oral treatment of myasthenia gravis. The bromide is used in the oral tablet form as it is comparatively nonhygroscopic.

Dosage—15 mg., three times daily. If necessary, the dose may be cautiously increased to 30 mg. three times daily.

HOFFMANN-LA ROCHE, INC.

Tablets Prostigmin Bromide 0.015 Gm

U. S. patent 1,905,990 (April 25, 1933, expires 1950) U. S. trademark 293,889



For description and standards see the U. S. Pharmacopeia under Neostigmine Methylsulfate and Neostigmine Methylsulfate Injection.

Actions and Uses—See general statement on Neostigmine.

Dosage—Prevention of postoperative distention: small doses of the 1:4,000 solution are administered subcutaneously or intramuscularly at frequent intervals. Injections are begun twenty-four hours before the operation if feasible, otherwise as soon as possible, and repeated in 1 cc. doses every four to six hours until the second or third postoperative day. Treatment of postoperative distention: usually one or two ampuls of the 1:2,000 solution, as required, are administered subcutaneously or intramuscularly. Experimental use in the treatment of myasthenia gravis: only one ampul of the 1:2,000 solution is administered initially, the size and interval of the subsequent doses to be given as indicated by the degree and duration of the response to the initial dose. The course of treatment usually consists of from one to four ampuls (from 0.5 to 2 mg. of neostigmine methylsulfate).

HOFFMANN-LA ROCHE, INC.

Solution Prostigmin Methylsulfate 1:2,000 and 1:4,000: 1 cc. ampuls.

U. S. patent 1,905,990 (April 25, 1933, expires 1950) U. S. trademark 293,889

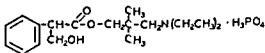
ANTIPARASYMPATHOMIMETIC AGENTS

the heart, an effect which, with proper dosage, is much like that of cutting both vagus nerves and usually amounts to an acceleration. The dilation of the pupil and paralysis of accommodation by atropine are similar to the effects of cutting the oculomotor

Atropine Derivatives and Analogues

SYNTHETIC MYDRIATICS

The usefulness of atropine is somewhat diminished by the fact that it affects, simultaneously, so many organs; on the eye its effects continue much longer than is in many cases desirable. Many attempts have been made to secure drugs of the atropine type with more specific actions or drugs that have a more transitory effect upon the eye. One of these drugs (homatropine) is a synthetic alkaloid analogous to atropine, the only difference being that it contains mandelic acid instead of tropic acid in combination with tropine; eucatropine is a combination of mandelic acid and a base similar to that contained in beta-eucaine.



For tests and standards, see Section B.

Actions and Uses—The actions of amprotropine phosphate are similar to those of atropine. However, amprotropine phosphate acts to a certain extent directly on smooth muscle in addition to its inhibitory effect on parasympathetic endings. It does not depress salivary secretion as actively as atropine or induce mydriasis as readily, and its inhibitory action on the parasymp-

Dosage.—For oral administration, one tablet (50 to 100 mg.) three or four times a day. In some cases of Parkinson's disease (paralysis agitans) as much as 2400 mg. in divided doses has

been given within 24 hours without serious toxic symptoms. For subcutaneous or intramuscular administration, 1 cc of ampro tropine phosphate solution (representing 10 mg of ampro tropine phosphate) three times a day.

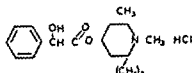
HOFFMANN LAROCHE, INC.

Syntropan (Powder) 5 Gm vials

Tablets Syntropan 50 mg and 0.1 Gm

U S patents 1,932,341 (Oct 24 1933 expires 1950) and 1,987,546 (Jan 8 1935 expires 1952) U S trademark 308 080

EUCATROPINE HYDROCHLORIDE U S P — Euphthalmine Hydrochloride (SCHERING & GLATZ Div Wm R WARNER) — When dried over sulfuric acid for 4 hours contains not less than 86 per cent and not more than 89 per cent of eucatropine ($C_{17}H_{25}O_3N$) U S P The structural formula may be represented as follows



For description and standards see the U S Pharmacopeia under Eucatropine Hydrochloride

Actions and Uses—Eucatropine hydrochloride produces prompt mydriasis free from anesthetic action, pain, corneal irritation or in normal individuals increase in intra-ocular tension. It should be noted however that eucatropine hydrochloride shares with other mydriatics the hazard of precipitating glaucoma in anatomically predisposed individuals. It has little or no effect on accommodation and such effect as it has disappears more rapidly than that of atropine, cocaine, homatropine, etc. In its effects on the general system eucatropine hydrochloride very closely resembles atropine. It is useful as an aid in ophthalmoscopic examination in place of atropine, homatropine, etc.

Dosage.—From 2 to 3 drops of a 5 or 10 per cent solution and instilled into the eye at two 5 minute intervals according to the age of the patient and the nature of the case.

SCHERING & GLATZ DIVISION OF Wm R WARNER & Co INC.

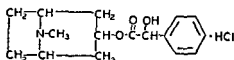
Euphthalmine Hydrochloride (Powder) 0.5 Gm and 1 Gm.

U S. patent 663 754 (exp red) U S trademark 33 541

WERNER DRUG & CHEMICAL CO

Eucatropine Hydrochloride (Powder) Bulk, 0.5 Gm., 1 Gm, 5 Gm and 30 Gm.

HOMATROPINE HYDROCHLORIDE.—The hydrochloride of the alkaloid homatropine, obtained by the condensation of tropine and mandelic acid. The structural formula of homatropine hydrochloride may be represented as follows:



For tests and standards, see Section B.

Actions and Uses.—Homatropine hydrochloride is useful when a paralysis of accommodation is necessary. Recovery from this cycloplegic effect is complete in 3 to 4 hours.

in the case

action. Ex-

disposed to

action not

conjunctival vessels and on injection lowers the blood pressure but affects the parasympathetic system, for instance the vagus, much less than atropine; five to ten times as high a dosage is necessary to paralyze.

Dosage—It is applied to the eye in 1 per cent solution

MERCK & Co., Inc

Homatropine Hydrochloride (Crystals): Bulk.

IDE-N. F.—Nova-

(Do).—The methyl-

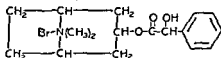
dried at 105 C. for

3 hours, contains not less

3.85 per cent of N and not less than 21.3 per cent and not more

than 21.9 per cent of Br."—N. F. The structural formula may

be represented as follows.



For description and standards see The National Formulary under Homatropine Methylbromide and Homatropine Methylbromide Tablets

Actions and Uses—Homatropine methylbromide is proposed for use in the treatment of gastro-intestinal spasm and hyperchlorhydria. Animal experimentation has shown it to be less active than atropine but also less toxic.

Dosage—Adults: one or two tablets three times daily before meals; children and infants: according to age.

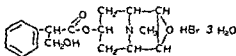
CAMPBELL PRODUCTS, INC.

Tablets Novatrin: 25 mg.

ENDO PRODUCTS, INC.

Mesopin Tablets • 25 mg

SCOPOLAMINE HYDROBROMIDE—U. S. P.—Hyoscine Hydrobromide—The hydrobromide of an alkaloid obtained from plants of the *Solanaceae*—The structural formula may be represented as follows



For description and standards see the U S Pharmacopeia under Scopolamine Hydrobromide

Actions and Uses—It is used mainly as a sedative in psychiatry and surgery and also locally as a mydriatic in cases which display an idiosyncrasy toward atropine. Its peripheral (but not its central) action is similar to that of atropine but its effects are more transient.

Dosage—0.5 mg

"Caution—Scopolamine Hydrobromide is extremely poisonous"—U S P

MERCK & Co, INC.

Scopolamine Hydrobromide (Crystals) • 65 mg, 0.3 Gm and 1 Gm vials

Scopolamine Hydrobromide (Powder) 65 mg, 0.3 Gm. and 1 Gm vials

SCOPOLAMINE STABLE—Hoffmann-LaRoche—Scopolamine—An aqueous solution of pure scopolamine hydrobromide protected against decomposition by the addition of 10 per cent of mannite

For tests and standards, see Section B

Actions, Uses and Dosage—The same as those of scopolamine hydrobromide U S P

HOFFMANN LA ROCHE INC.

Solution Scopolamine (Stable) 0.3 mg 1 cc and 0.6 mg, 1 cc ampuls. Each cc contains 0.3 mg of scopolamine hydrobromide in a 10 per cent aqueous solution of mannite

Cardiovascular Agents

Cardiovascular agents comprise those drugs whose action upon the heart and other muscular portions of the vascular system is such as to affect either the total output of the heart or the distribution of blood to particular branches of the circula-

(1) digitalis and other
in and output of the
the nitrites.

tem Stimulants. Ethyl alcohol, sometimes employed internally in the form of "spirits" for its vasodilating action, is more reliable as a beverage than as a medicinal agent.

DIGITALIS AND DIGITALIS-LIKE PRINCIPLES AND PREPARATIONS

The digitalis group embraces many crude drugs and proximate principles which have a peculiar action on cardiac muscle. Digitalis, strophanthus and squill have been investigated far more than the others, and we are much better informed concerning their actions; from them are derived nearly all the active principles and proprietary preparations of the group which have been included in N. N. R.

Digitalis and digitalis-like principles may be administered by mouth, by injection and as described under the accepted preparations. The U. S. Pharmacopeia recognizes a solution of digitalis for injections, but it should be remembered that the optimum frequency of repetition of the intravenous dose of different digitalis preparations varies widely, even with those of equal potency, depending on several factors, especially on difference in persistence of action. The physician must learn the proper intravenous dosage of any preparation of digitalis which he employs.

Cardiac Action—The cardiac action of the individual drugs of the group is similar. They all act directly on heart muscle. They diminish the size of the heart as measured by the x-ray silhouette. While they increase the output of diseased hearts, they diminish that of normal hearts. The margin between therapeutic and toxic actions on the heart is believed by some to differ for different substances, although the weight of evidence

indicates that the margin of safety does not differ. In patients with auricular fibrillation they all slow the heart rate by a combination of a direct action on the heart muscle and an indirect vagal action. The larger the dose the more pronounced the direct action. The proportion of these two actions is similar for the different members of the whole group.

Differences exist chiefly in relation to their absorption from the gastrointestinal tract, their speed of elimination, and their local emetic action. Their potencies differ, and difficulties arise from faulty standardization.

Standardization—There are various methods for the standardization of this group of drugs, involving the use of several species of animals the frog the guinea pig etc. The U. S. Pharmacopeia requires that digitalis be standardized against the U. S. P. Digitalis Reference Standard by the official cat method which involves intravenous injection into cats until death occurs by cardiac arrest. The available evidence indicates that the cat method yields results more nearly applicable to man than those of the frog method. The Standard preparation and the unknown are similarly injected into groups of animals and the average fatal doses of the two are compared. The unknown is then adjusted so that 0.1 Gm. has the potency of 0.1 Gm. of the Standard or 1 U. S. P. Digitalis Unit. Since the U. S. P. Digitalis Unit is the result of an assay by the cat method and represents an improved technique in bioassay the expression of potency in U. S. P. Digitalis Units is preferable to the older expression in terms of cat units. By direct testing it has been found that 1 U. S. P. Digitalis Unit is equivalent approximately to 1.3 "cat units," using the cat method technique of the Pharmacopeia.

In the case of digitalis leaf and the tincture the results of comparison by means of the cat method agree fairly satisfactorily with similar comparisons in humans to whom the drugs are given by oral administration but there is less agreement in the case of purified materials because of wide differences in their absorption from the gastrointestinal tract and the intravenous method does not distinguish absorbable from nonabsorbable material. Hence a U. S. P. Unit of different specimens of the Digitalis Leaf or Tincture Digitalis may be counted upon to produce substantially similar results when given orally to man (although there are some exceptions) but not so in the case of purified materials.

Differences in Emetic Action—The digitalis principles are irritant to mucous membranes and subcutaneous tissues. When given in large doses the local irritation in the gastrointestinal tract may be sufficient to cause nausea and vomiting within several minutes to an hour or two. These drugs however are rarely administered in such doses and when given in the usual smaller doses the local irritant action is insufficient to cause nausea or vomiting. The nausea or vomiting which follows the customary doses of digitalis is due to a systemic action after

absorption and represents a toxic symptom. The seat of this action is the vomiting center which is affected indirectly through the heart. The emetic action is roughly proportional to the cardiac effects of the various members of the group and when this

need for reducing the size of the dose.

Differences in Absorption.—Digitalis contains a mixture of glycosides, some of which are rapidly, and others poorly absorbed from the gastrointestinal tract. After an oral dose only about one fifth of the potent materials produce a systemic action, as shown by the fact that it requires only about one-fifth as much for intravenous as for oral administration to produce the same results. Digitoxin is almost completely absorbed, whereas other fractions may not be absorbed at all. The potent principles of strophanthus are so poorly absorbed from the gastrointestinal tract that they are undesirable for oral administration and are used chiefly by intramuscular or intravenous injection in small doses.

Differences in Cumulative Action.—All the digitalis bodies in common use are cumulative. Not all show the same degree of cumulative action. Some are more rapidly eliminated than others, especially pro-
xin. It is much

less in the (

Intravenous of the intra-
venous dose varies widely,
even with those of equal potency, depending on several factors, especially on difference in persistence of action. The physician must learn the proper intravenous dose of any preparation of digitalis which he employs.

The disadvantages of all the drugs of the digitalis group have served as a constant stimulus in the search for pure principles suitable for intravenous or intramuscular administration. Pure

or Digalen.

Proprietary Digitalis Preparations.—Several digitalis preparations have been introduced into therapeutic use with the claim that they are composed either of pure principles, or of purified extracts of digitalis, and that they are devoid of certain disadvantages possessed by the preparations of the U. S. Pharmacopeia. The Council urges on clinicians the necessity of acquiring skill in the use of digitalis materials by the careful observation of a very few members of the group, rather than

to try to use without discrimination the large number of preparations which are offered

DIGALEN (HOFFMANN LAROCHE)—The cardioactive principles of digitalis as isolated by Cloetta. It is standardized by a modification of the intravenous cat method of Hatcher and Brody

For tests and standards see Section B

Actions and Uses—The same as those of digitalis

Dosage—The average maintenance dose of this preparation (in 30 cc. vials) is from 1 to 2 cc (0.8 to 1.6 U S P unit). The maximum daily dosage is 6 cc. The average dose of tablets digalen is from 0.4 U S P to 0.8 U S P unit three times daily. The average dose of the injectable solution of this preparation is 2 cc.

Preparation—

The dried and finely powdered leaves of digitalis are extracted with diluted alcohol; then the extract is mixed with lead acetate solution in order to remove chlorophyll and resins and filtered. From this filtrate the excess of lead is precipitated with sodium sulfate and the alcohol distilled off *in vacuo*. From the remaining aqueous solution, the active derivative of digitalis contained in digalen is extracted by ethereal solvents and precipitated afterward in an amorphous condition according to a special secret method. The several dosage forms are standardized by the intravenous cat method.

HOFFMANN LAROCHE, INC.

Solution Digalen Injectable 2 cc ampuls. Each 2 cc represents 1 cat unit, in 8 per cent alcohol equivalent in potency to approximately 81 mg U S P Digitalis Reference Standard = 0.8 U S P Digitalis Unit.

Solution Digalen 30 cc. vials. Each 1 cc. represents 1 cat unit, in 26 per cent alcohol equivalent in potency to approximately 81 mg U S P Digitalis Reference Standard = 0.8 U S P Digitalis Unit.

Tablets Digalen $\frac{1}{2}$ cat unit and 1 cat unit, respectively equivalent in potency to 40 mg U S P Digitalis Reference Standard = 0.4 U S P Digitalis Unit and 81 mg U S P Digitalis Reference Standard (1942) = 0.8 U S P Digitalis Unit.

U S trademarks 43 593 and 83 738

DIGIFOLIN (CIBA)—A digitalis preparation containing the therapeutically desirable constituents of digitalis leaf. It is standardized by the U S P Digitalis assay method.

For tests and standards see Section B

Actions and Uses—The same as those of digitalis

Dosage—In the majority of cases in which digitalis therapy is indicated the oral administration of 0.8 U S P units in the form of tablets or of an oral solution of this preparation four

Suppositories Digilanid: 0.5 mg. (1.2 U. S. P. units).

Tablets Digilanid: 0.33 mg. (0.8 U. S. P. unit).

U. S. patents 1,923,490 (Feb. 19, 1931; expires 1948) and 1,923,491 (Aug. 22, 1931; expires 1948). U. S. trademark 291,301.

DIGITAN (MERCK).—A purified extract of digitalis containing the active principles in the same proportions as they exist in the whole leaf. In the purified extract, 85 per cent of the inactive substances present in the ordinary extract have been removed and it is free from digitonin. The extract is physiologically standardized according to the official U. S. P. procedure.

For tests and standards, see Section B.

Actions and Uses.—The same as those of digitalis.

Dosage.—The same as that of digitalis.

Preparation.—

The preparation is obtained by removing all antiseptic constituents from the extract of digitalis, and then adding a small amount of sugar.

MERCK & Co., INC.

Digitan (Powder).

Solution Digitan: 0.1 Gm., 1 cc. ampuls.

Tablets Digitan: 0.1 Gm

U. S. patent 943,578 (Dec. 14, 1909; expired). U. S. trademark 138,484.

DIGITOL (SHARP & DOHME).—Tincture of Digitalis (Fat-Free).—A biologically standardized, fat-free tincture of digitalis, corresponding in drug strength to tincture of digitalis-U. S. P., and containing 73 per cent alcohol.

Actions and Uses.—The same as those of digitalis. This preparation of digitalis was sent the claim of only advantage of very clear mixture

Dosage.—From 0.3 to 1 cc.

Preparation.—

Digitalis which has previously been subjected to percolation with petroleum benzene is extracted by percolation with hydro-alcoholic menstruum in the usual way.

The tincture is a brownish-green liquid having a characteristic and highly alcoholic odor and a bitter taste. Each cc. represents one U. S. P. Digitalis Unit.

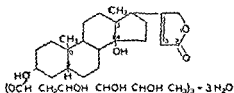
SHARP & DOHME, INC.

Digitol (Liquid).

U. S. trademark 208,315.

DIGITOXIN U S P.—Digitaline Nativelle (VARICK)

—“Digitoxin is either pure digitoxin ($C_{41}H_{64}O_{13}$) or a mixture of radioactive glycosides obtained from *Digitalis purpurea* Linné (Fam. *Scrophulariaceae*) and consisting chiefly of digitoxin. The potency of digitoxin assayed biologically corresponds to the potency of an equal weight of U S P Digitoxin Reference Standards’ U S P. The structural formula for digitoxin as far as it is known, may be represented as shown below where the sugar residue shown attached at position 3 is digitoxose



For description and standards see the U S Pharmacopeia under Digitoxin, Digitoxin Injection and Digitoxin Tablets

Actions and Uses.—Digitoxin, the chief active glycoside of *Digitalis purpurea* was used by Nativelle in 1868 and first reported in the literature in 1869. It is available in crystalline form sufficiently pure to be administered by weight. It is almost completely absorbed from the intestinal tract and a given dose produces practically the same therapeutic effect whether given by mouth or by vein. Nausea or vomiting due to local action are almost never encountered. In oral administration 1 mg of digitoxin exerts approximately the same therapeutic action as one gram of U S P XIII *Digitalis*. The full digitalizing effect of the drug following oral administration is obtained about as quickly as when the same dose is administered intravenously and thus the drug does not need to be administered intravenously in the average patient, but may be given by vein to comatose patients and to patients who cannot take oral medication for other reasons.

Dosage.—Most patients can be digitalized by the administration of not more than 12 mg, although a few may require a larger amount while others will show some sign of intoxication from even this quantity. For patients who have received no digitalis in any form for at least two weeks the average dose of 12 mg may be given at one time but under most conditions it is wiser to begin with 0.6 mg, administering subsequent doses of 0.4 mg down to 0.2 mg on the same day then following with a daily maintenance dose, such maintenance may usually be accomplished by giving daily doses of 0.2 mg. Digitalization may also be accomplished by administering each day a dose of 0.2 mg for a period of one to three weeks even when no larger initial dose has been given.

Caution.—Digitoxin is extremely poisonous.

ABBOTT LABORATORIES

Solution Digitoxin: 0.2 mg. per cc., 1 cc. ampuls.

Tablets Digitoxin: 0.1 mg. and 0.2 mg.

THE CENTRAL PHARMACAL COMPANY

Tablets Digitoxin: 0.2 mg.

S. F. DUREST & COMPANY, INC.

Tablets Digitoxin: 0.1 mg. and 0.2 mg.

MCNEIL LABORATORIES, INC.

Solution Digitoxin: 0.2 mg. per cc., 1 cc. ampuls.

THE WM. S. MERRELL CO.

Tablets Unidigin: 0.1 mg. and 0.2 mg.

U. S. trademark 422,580.

PREMO PHARMACEUTICAL LABORATORIES, INC.

Tablets Digitoxin: 0.1 mg. and 0.2 mg.

CARROLL DUNHAM SMITH PHARMACAL CO.

Tablets Digitoxin: 0.2 mg.

R. J. STRASENBURGII CO.

Tablets Digitoxin: 0.1 mg., and 0.2 mg.

VARICK PHARMACAL CO., INC.

Solution Digitaline Nativelle: 0.2 mg., 1 cc. ampuls and 0.4 mg., 2 cc. ampuls

Tablets Digitaline Nativelle: 0.1 mg. and 0.2 mg.

WYETH INCORPORATED

Solution Purodigin: 1 cc. ampuls and 1 cc. Tubex (U. S. trademark 406,632). Each cc. contains 0.2 mg. of digitoxin in 40 per cent alcohol solution.

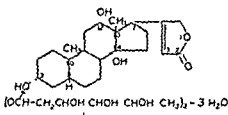
Tablets Purodigin: 0.1 mg. and 0.2 mg.

U. S. trademark 411,271.

DIGOXIN-U. S. P.—"A glycoside which may be prepared from the leaves of *Digitalis lanata*, Ehrh (Fam. *Scrophylariaceae*)." U. S. P.

The crude lanatosides from the leaves are separated by physical methods into lanatosides A, B and C. Digoxin is formed from lanatoside C by hydrolytic removal of acetyl and glucose groups. The potency of Digoxin, assayed biologically, corresponds to the potency of an equal weight of U. S. P. Digoxin Reference Standard

The structural formula of digoxin, as far as it is known, may be represented as shown below, where the sugar attached at position 3 is digitoxose.



For description and standards see the U S Pharmacopeia under Digoxin Digoxin Injection and Digoxin Tablets

Actions and Uses—The actions and uses are closely similar to those of digitalis U S P. As a purified substance it is claimed to have particular usefulness when rapid digitalization is desired. Its action is manifest usually within a few hours when administered by mouth and within a few minutes when given intravenously.

Dosage—Before administering a large dose of digoxin, it must be ascertained that no drug of the digitalis group has been given within two weeks.

For rapid digitalization by the oral route, an initial dose of approximately 0.75 mg. may be administered, followed by doses of 0.25 to 0.75 mg. at six hour intervals until the ventricular rate lies between 60 and 70 or the maximum therapeutic effect is obtained, or toxic symptoms appear.

h an intra-
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one to two
six hours,
y be given

"Caution—Digoxin is extremely poisonous" U S P

BURROUGHS WELLCOME & Co., Inc.

Tabloid Digoxin 0.25 mg.

Solution Digoxin, 0.05% 1 cc ampuls Contains 0.5 mg of digoxin per cc. in 70 per cent alcohol solution.

U S trademark 76 731

GITALIN (AMORPHOUS)—A glycosidal constituent of *Digitalis purpurea* Linné prepared according to the method of Kraft.

For tests and standards, see Section B

Actions and Uses.

Dosage.—Full after a
total dosage of 4 These
effects may be obtained by the administration of two to three
tablets per day for three or four days. The same precautions
should be taken with gitalin as with any digitalis preparation
or digitaloid drug. Should toxic symptoms, such as nausea or
vomiting, occur during the course of digitalization, administra-
tion of the drug should be discontinued. After the desired clinical
effects have been induced, the patient may be placed on a
maintenance dose of 0.25 mg. to 0.75 mg. (one-third to one
tablet) daily. The amount varies according to the individual
requirements of the patient. Gitalin (amorphous) is less cumula-

strength.

Preparation.—

Dried and ground leaves of *Digitalis purpurea* Linné are extracted with cold, distilled water. This aqueous infusion is then treated with basic lead acetate and the lead subsequently removed by precipitation with sodium sulfate. The resulting filtrate is agitated with chloroform and allowed to separate. From the chloroform extract the gitalin (amorphous) substance is precipitated by means of petroleum ether. The precipitate is subjected to further purification and finally dried in vacuo. The entire process of extraction and purification is conducted without the aid of heat.

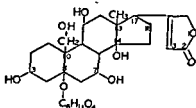
RARE CHEMICALS, INC.

Tablets Gitalin (Amorphous): 0.75 mg. Each tablet is scored into segments of 0.25 mg. for convenience in regulation of the daily maintenance dose.

Related Digitalis Principles

OUABAIN-U. S. P.—G. Strophanthin.—“A glycoside obtained from *Adonis vernalis* L. (Wall et Hook.)”

The structural formula of ouabain, as far as it is known, may be represented as shown below, where the sugar attached at position 5 is rhamnose.



For description and standards see the U. S. Pharmacopeia under Ouabain and Ouabain Injection.

Actions and Uses—The pharmacologic action of ouabain is probably qualitatively identical with that of the official strophanthus or strophanthin but ouabain is more active than the official strophanthin when injected intramuscularly or intravenously. This action develops more rapidly, the drug is more quickly excreted and shows less tendency to cumulative action than does digitalis.

Ouabain is used only for injection in place of strophanthus or strophanthin as a substitute for digitalis.

Dosage—Ouabain is absorbed so slowly and so irregularly from the alimentary canal that the oral administration of the drug is not to be recommended and is even considered unsafe.

For intravenous or intramuscular administration, the dose is 0.5 mg. and this dose should not be repeated as a rule within less than 24 hours. It is best employed dissolved in from 4,000 to 8,000 parts of isotonic solution of sodium chloride. When the intramuscular or intravenous dose is to be repeated within less than 24 hours a smaller amount should be administered.

Since ouabain solution may deteriorate rapidly, when sterilized in glass which yields traces of alkali, only solutions which have been kept in alkali free glass containers should be used.

Caution—Ouabain is extremely poisonous.

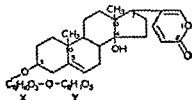
MERCK & Co., Inc.

Ouabain (G-Strophanthin) (Powder).

CARROLL DUNHAM SMITH PHARMACEUTICAL COMPANY

Solution Ouabain 0.1 mg., $\frac{1}{2}$ cc. ampuls and 0.5 mg., 2 cc. ampuls.

SCILLAREN (Savdoz)—A mixture of two natural glycosides (component A and component B) occurring in fresh squill *Urginea maritima* in the proportions in which they exist in the fresh crude drug, namely about 2 parts of A to 1 part of B. The completely dried preparation contains approximately 98 per cent of the active glycosides. The preparation dried in a high vacuum at 78° C. for 15 hours loses not more than 6 per cent of its weight. The structural formula of component A as far as it is known may be represented as shown below, where X = rhamnose and Y = glucose.



For tests and standards, see Section B.

Actions and Uses.—The cardiac action of this preparation is essentially similar to that of digitalis, but this action is apparently less persistent than that of digitalis.

Dosage.—1.6 mg. orally from three to four times daily until compensation is established or until minor toxic symptoms are induced. After compensation is established, 0.8 mg. may be administered from two to four times daily.

SANDOZ CHEMICAL WORKS, INC.

Tablets Scillaren: 0.8 mg.

Solution Scillaren: Each cc. represents 0.8 mg. of the preparation. The oral solution contains 25 per cent alcohol and 20 per cent glycerin by weight and the solution for injection 6 per cent alcohol and 15 per cent glycerin by weight.

U. S. patent No. 1,516,552 (Nov. 25, 1924; expired) and No. 1,579,338 (April 6, 1926; expired). U. S. trademark 173,046.

Dosage.—2 cc. (40 drops) three to four times daily; after compensation is established, 1 cc. (20 drops) two to four times daily. A dropping device is supplied with each package, designed to yield 20 drops per cubic centimeter.

SCILLAREN-B (SANDOZ).—The amorphous component of the natural mixture of the glycosides occurring in squill, *Urginea maritima*. The completely dried component B contains approximately 99.5 per cent active glycosidal substance. Component B dried in a high vacuum at 78 C. for 15 hours loses not more than 5 per cent of its weight.

For tests and standards, see Section B.

Actions and Uses.—The same as those of Scillaren.

Dosage.—This preparation is for intravenous administration when immediate action is indicated. Not more than 0.5 mg. of this drug should be injected intravenously within 24 hours.

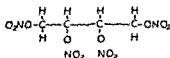
SANDOZ CHEMICAL WORKS, INC.

Solution Scillaren-B: 0.5 mg., 1 cc. ampuls. The oral solution contains 25 per cent alcohol and 20 per cent glycerin by weight and the solution for injection 6 per cent alcohol and 15 per cent glycerin by weight.

U. S. patent 1,516,552 (Nov. 25, 1924; expired) and 1,579,339 (April 6, 1926; expired). U. S. trademark 173,046.

ORGANIC NITRATES

The esters of nitric acid and the higher alcohols (glycerin, propane blood vit (nitrite) nitrite, etc.) are converted in the body of nitrites from them.



For description and standards see the U S Pharmacopeia under Erythrityl Tetranitrate Tablets

Actions and Uses—Erythrityl tetranitrate is a vasodilator like nitroglycerin. Its action is slower and more lasting, beginning in fifteen minutes and persisting for three or four hours.

The action of erythrityl tetranitrate is too slow to give satisfactory relief to acute attacks of angina pectoris. It is reported as useful as a prophylactic in preventing anginal pain if administered shortly before exercise, but when given routinely to prevent attacks the results of carefully controlled studies have been negative. Given at bedtime it may have some value in those attacks which are prone to occur during the night in very severe cases of this disease.

Although erythrityl tetranitrate causes a prolonged fall of blood pressure in certain cases of hypertension, the reduced pressure cannot be maintained by repeated administration of this drug. This invalidates its use in the prolonged treatment of hypertension. Its efficacy in peripheral vascular disease is also questionable because the fall in blood pressure calls forth vasoconstrictor reflexes. These reflexes compete with the dilator influence of erythrityl tetranitrate and often overcome it, resulting in peripheral vasoconstriction. This drug often causes severe headaches.

Dosage—From 30 mg to 60 mg every four to six hours. Pure erythrityl tetranitrate is a crystalline mass, which explodes on percussion, hence it is marketed chiefly in the form of tablets. Sold in the form of tablets only.

BURROUGHS WELLCOME & Co, INC.

Tabloid Erythrityl Tetranitrate 16 mg and 32 mg

U S trademark 76 731

MERCK & Co, INC.

Tablets Erythrol Tetranitrate 16 mg and 32 mg

creases the refractory period of the auricular muscle and depression is upon the cardiac muscle, which is depressed. The auriculoventricular conduction time is lengthened. Quinidine is used to restore the normal rhythm of the heart in cases of auricular fibrillation. This has been brought about in approximately 50 per cent of the reported cases in which the drug has been used. While restoration of normal rhythm in cases of auricular

tion of the arrhythmia is known to have been comparatively short. However, the drug has often been successfully used to terminate auricular fibrillation of many years duration, and accidents due to its use are rare. It is least effective in cases of fibrillation with marked cardiac insufficiency. It is useful in slowing the rate in ventricular tachycardia. Quinidine is not without some unpleasant and even dangerous effects. Some patients appear much more susceptible to its intoxication than others. The untoward symptoms brought about by its use in these patients are nausea, vomiting, convulsions, palpitation, headache, faintness and flushing. In most cases following the administration the normal rhythm is restored. In a few instances the drug is re-administered in such instances, such as (ventricular tachycardia) of therapy. To a normal rhythm sudden death stopped. The drug is rapidly eliminated.

Dosage.—Quinidine is generally administered as quinidine sulfate. Commonly 0.2 Gm of quinidine sulfate is given as a maintenance dose and is repeated after two hours to determine here are no symptomatic administration Gm. to 0.4 Gm. is one to three days. Normal rhythm can be effected, the change occurs after from one to three days' treatment. The maximum dose per day advised by most authors is from 1 to 2 Gm. In ventricular tachycardia following cardiac infarction, larger doses are sometimes required and are well tolerated. If toxic symptoms occur, the administration of the drug should be discontinued. Intravenous administration is dangerous and is not recommended.

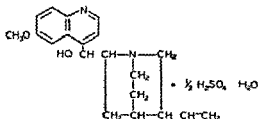
MALLINCKRODT CHEMICAL WORKS

Quinidine (Powder): Bulk.

MERCK & Co INC

Quinidine N F V (*Crystals or Powder*) Bulk

QUINIDINE SULFATE U S P—The sulfate of an alkaloid obtained from the bark of the stem or of the root of various species of *Cinchona* and their hybrids and from *Remyia pedunculata* Fluckiger (Fam. *Rubiaceae*) U S P The structural formula may be represented as follows



For description and standards see the U S Pharmacopeia under Quinidine Sulfate and Quinidine Sulfate Tablets

Actions and Uses—See article on Quinidine

Dosage—See article on Quinidine Quinidine sulfate may be administered in the form of cachets capsules pills or tablets

ABBOTT LABORATORIES

Capsules Quinidine Sulfate 0.2 Gm

DAVIES ROSE & COMPANY LTD

Tablets Quinidine Sulfate 0.2 Gm.

MALLINCKRODT CHEMICAL WORKS

Quinidine Sulfate (*Powder*) Bulk

MERCK & Co INC.

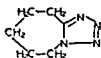
Quinidine Sulfate (*Crystals*) Bulk

Central Nervous System Stimulants

This chapter describes a number of drugs that stimulate the brain and spinal cord. Injections of caffeine and sodium benzoate, for instance, and inhalations of carbon dioxide with air or oxygen are practically never given for any other purpose. Oxygen itself is not strictly a stimulant, but is included here for convenience. Picrotoxin has also been included because it is particularly valuable in combating the depression of severe barbiturate intoxication.

Certain autonomic drugs that produce conspicuous central stimulating effects are also included here. Theophylline ethylenediamine, which is useful on combating Cheyne-Stokes respiration because of its central stimulating action, is described with other theophylline and theobromine preparations in the chapter on Diuretics.

METRAZOL (BILHUBER KNOLL).—Pentamethylenetetrazol. The structural formula may be represented as follows:



For tests and standards, see Section B.

Actions and Uses.—The action of pentamethylenetetrazol is primarily stimulating to the midbrain, the medullary centers and perhaps the spinal cord. Its action following injection intravenously or subcutaneously is induced promptly. Although pentamethylenetetrazol has been used to stimulate the vasomotor and respiratory centers, this action is observed clinically usually only when the dose approaches the convulsive level. Pentamethylenetetrazol is effective in accelerating recovery from narcotic de-

then should be given more slowly. An attempt should be made to hold the action at or just below this level until recovery of respiratory and cerebral function is manifest.

Pentamethylenetetrazol has come into extensive use in the treatment of mental disorders in doses which induce convulsions. For this purpose, it is safer than insulin hypoglycemia. Reports have appeared of minor fractures of the vertebrae, without paralysis induced by these convulsions. These may be prevented by the cautious use of curare prior to the use of pentamethylene-tetrazol. Because of its difficulties and dangers, convulsive treatment should be instituted only by psychiatrists or in an institution where the necessary care can be given.

It has also been reported to be of value in emergencies due to cardiovascular collapse, again without valid evidence of its effectiveness.

Dosage—Intramuscularly, subcutaneously, or intravenously, from 0.1 to 0.3 Gm. repeated as required, orally, from 0.1 to 0.3 Gm. several times daily. For narcotic poisoning very large doses may be required, and the dosage should be governed solely by the clinical effect.

BILHUBER KNOLL CORP.

Solution Metrazol: 1 cc. and 3 cc. ampuls. Each 1 cc. contains 0.1 Gm. of pentamethylenetetrazol in aqueous solution with 0.1 per cent sodium phosphate.

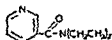
Solution Metrazol 10%: 30 cc. bottles. An aqueous solution containing pentamethylenetetrazol, 0.1 Gm. per 1 cc. for oral use.

Solution Metrazol 10%: 30 cc. bottles. A sterile solution containing pentamethylenetetrazol 0.1 Gm. per cc. for parenteral administration.

Tablets Metrazol: 0.1 Gm.

U. S. patent 1,599,493 (Sept. 14, 1926 expired). U. S. trademark 242,687.

NIKETHAMIDE—*N,N*-Diethylpyridine-3-carboxamide—*N,N*-diethyl nicotinamide. The structural formula may be represented as follows:



For tests and standards, see Section B.

Actions and Uses—Experiments involving several species of animals indicate that the action of nikethamide is mainly on the

ABBOTT LABORATORIES

Solution Nikethamide 25% W/V 15 cc ampul

GEORGE A. BREON & COMPANY INC.

Solution Nikethamide 25% W/V 15 cc and 480 cc bottles for oral administration

Solution Nikethamide 25% W/V 15 cc ampuls

BUFFINGTON S. INC.

Solution Nikethamide 25% W/V 2 cc. and 5 cc. ampuloids

THE DRUG PRODUCTS CO. INC.

Solution of Nikethamide 25% W/V 15 cc. ampuls 30 cc vials Preserved with chlorobutanol 0.5 per cent.

ENDO PRODUCTS INC.

Solution Nikethamide 25% W/V 15 and 5 cc. ampuls and 15 cc vials for oral administration

FLINT EATON & COMPANY

Solution Nikethamide 25% W/V 2 cc. ampuls

THE NATIONAL DRUG CO.

Solution Nikethamide 25% 5 cc ampuls 15 cc and 120 cc bottles for oral administration Preserved with chlorobutanol 0.5 per cent

PREMO PHARMACEUTICAL LABORATORIES

Solution Nikethamide 25% W/V 15 cc 45 cc. and 480 cc bottles for oral administration 15 cc and 5 cc. ampuls for parenteral administration

CARROLL DUNHAM SMITH PHARMACEUTICAL CO.

Solution Nikethamide 25% W/V 15 cc. vials

SMITH DORSEY COMPANY

Solution Nikethamide 25% W/V 15 cc. ampuls

THE UPJOHN COMPANY

Solution Nikethamide 25% W/V 15 cc. and 10 cc ampuls and 887 cc bottles

WM. R. WARNER & CO. INC.

Solution Nikethamide 25% W/V 2 cc. and 5 cc. ampuls

PICROTOXIN U. S. P.—An active principle obtained from the seed of *Anamirta Cocculus* (Linné) Wight et Arnott (Fam. *Menispermaceae*) "U. S. P."

For description and standards see the U. S. Pharmacopeia under Picrotoxin and Picrotoxin Injection.

Actions and Uses.—Picrotoxin is a stimulant and convulsant acting chiefly on the higher centers. Thus if the midbrain and

Contraceptives

When protection from pregnancy is considered advisable, contraceptives are used to prevent passage of active spermatozoa from the vagina into the uterus. This is accomplished mechanically by occlusive devices, such as diaphragms, which lengthen the route which the spermatozoa must travel to reach the os, thereby assuring extensive exposure to a spermicidal jelly or cream. Contraceptive jellies and creams act as chemical

by a single user is often found to lead to greater acceptability

as been reviewed in a
The Journal, Dec 18,

CRITERIA FOR ACCEPTABILITY

Contraceptive Jellies, Creams and Other Chemical Agents and Syringe Applicators and Nozzles

For . . . , the Advisory . . . in Pharmacy . . . These have . . . emphasized that they may be changed from time to time. As the experience of the committee and the Council grows, improvements may appear desirable

1 The use of the word "contraceptive" need not be limited

to materials which will prevent conception on every occasion of use.

2. Evidence shall be furnished that use of the material decreases the incidence of pregnancy. This evidence may be secured in connection with occlusive devices unless the manufacturer's advertising is directed chiefly toward the use of the jelly or cream without such devices. It is desirable that each case reported should be observed for at least twelve months, and that the minimum of 75 patient-years of experience should be reported. If cases are excluded from the series on the basis of their being irregular users, the number excluded and the nature of the evidence justifying their exclusion should be stated.

3. Evidence shall be submitted that 100 or more couples have used the material on six or more occasions without subjective injury.

4. Evidence shall be submitted that 12 or more women have received vaginal applications of the recommended dosage on twenty-one successive days without subjective irritation or injury and without evidence of physical damage shown on speculum examination by a physician with special experience in this field. Inspection of the vagina once a week should be done as a protection to the patient in case the jelly proves to be irritating.

5. The quantitative formula from which the contraceptive mixture is prepared shall seem to the Advisory Committee to be safe and, presumably, effective.

6. The consistency shall be satisfactory to the committee. It shall not show separation into more liquid and more solid portions visible to the naked eye.

7. Evidence shall be submitted that the consistency is not substantially changed after storage for twelve months at 27 C.

8. The consistency shall be reasonably uniform from batch to batch.

9. The spermicidal time of the contraceptive material as measured by the method of Brown and Gamble (*Human Fertil.* 5:97 [Aug] 1940) with proportions of material, isotonic solution of sodium chloride and semen of 1:4.5 shall be thirty minutes or less as measured by the average of four or more tests.

10. The use of jellies or creams suggested by the manufacturer need not be limited to use in conjunction with an occlusive device.

11. If a syringe applicator or nozzle is furnished for use in connection with the jelly or cream, it shall be sufficiently translucent to permit the detection of air which might lead to inadequate dosage.

12. If a perfume is used, a quantitative statement of ingredients is desired.

Contraceptive Diaphragm or Cap

Criteria for the acceptability of contraceptive diaphragms and

accessory devices such as inserters and extractors have been adopted by the Council on Physical Medicine. The following physical devices accepted by the Council on Physical Medicine are intended to accompany or are available by the same distributors of accepted chemical contraceptives: Ortho Diaphragms, Ramses Diaphragms, Ramses Diaphragm Introducer, and Ramses Fitting Rings.

CONTRACEPTIVE PREPARATIONS

Jellies and Creams

Actions, Uses and Dosage—Jellies and creams for contraceptive use are usually introduced into the vagina by means of the

cream close to the occlusive device by means of a syringe applicator.

should a douche be taken within six hours of ejaculation.

As most of the contraceptive diaphragms are made of rubber which will deteriorate if exposed to greases, the jellies and creams used should not contain greasy substances such as lanolin and petrolatum.

Applicators are designed for ready filling from the container of contraceptive jelly or cream and for delivery under moderate pressure of the recommended dose (usually 5 cc.) into the upper vagina. They should be transparent to permit detection of air which might lead to inadequate dosage and if made of glass should be sufficiently thick walled to make breaking while in the vagina extremely improbable. The end should be blunt and sufficiently large to prevent entry into the urethra.

CONTRA CREME AND DIAPHRAGM CO

Contra Creme 635 Gm collapsible tubes. A stearic acid cream having a pH of 7.3 packaged from the formula

	Per Cent
Phenylmercuric acetate	0.06
Stearic acid	12.0
Triethanolamine	0.06
Glycol monostearate	3.5
Glycerin	2.5
Distilled water to make	100.00

Packaged with a Contra Applicator or in refill packages containing a tube of cream only.

U. S. trademark 355,838.

Contra Applicator: A transparent plastic syringe threaded at the blunt intravaginal end, to screw onto the tubes of Contra Creme, to permit filling by compression of the tube. The full capacity is 5 cc., the recommended dose.

DUREX PRODUCTS, INC.

Lactikol Creme: 56.5 Gm., 85 Gm. and 116 Gm. collapsible tubes. A water dispersible nonfatty stearic acid and glyceryl monostearate cream, having a pH of 4.9, prepared from the formula:

	Per Cent
Lactic acid	0.50
Stearic acid	15.00
Glycerol	0.60
.....	1.50
.....	7.50
.....	8.00
.....	0.07
Water sufficient to make.....	100.00

Packaged with a Lactikol Applicator or in refill packages containing a tube of cream only.

Lactikol Jelly: 62.5 Gm., 93.5 Gm. and 128 Gm. collapsible tubes. A water soluble jelly formed from tragacanth, karaya and acacia, having a pH of 4.15, prepared from the formula:

	Per Cent
.....	1.50
.....	0.05
.....	0.02
.....	0.20
.....	1.00
Glyceryl monoricinoleate	16.00
Glycerin	2.70
Tragacanth	1.00
Karaya	1.00
Acacia	0.04
Perfume	100.00
Water sufficient to make.....	

Packaged with a Lactikol Applicator or in refill packages containing a tube of jelly only.

Lactikol Plunger Applicator: A transparent plastic tube threaded at the blunt intravaginal end to screw onto the tubes of Lactikol Creme and Jelly to permit filling by compression of the tube. The full capacity is 5 cc., the recommended dose.

Lactikol Metri-Dose Applicator: A transparent glass tube graduated to permit delivery of from 5 to 8 cc., slightly constricted at the intravaginal end to fit the tubes of Lactikol Creme or Jelly, and fitted at the distal end with a rubber compression bulb with central wire spring device to permit adjustment of the volume of jelly or cream to be delivered.

EATON LABORATORIES, INC.

Lorophyn Jelly 92 Gm. collapsible tubes A water soluble jelly formed from tragacanth and purified Irish moss, having a pH of 7.5, prepared from the formula

.....	Per Cent
.....	0.05
.....	3.0
.....	0.05
.....	0.5
.....	1.8
.....	1.2
.....	8.0
.....	100.00

Packages containing a tube of jelly only **Lorophyn Jelly** Applicators are supplied in separate cartons

U S patent 2 436 184

Lorophyn Jelly Applicator A transparent plastic syringe threaded at the blunt intravaginal end, to screw onto the tubes of jelly, to permit filling by compression of the tube. The full capacity is 5 cc., the recommended dose

HOLLAND-RANTOS CO. INC.

Koromex Cream 78 Gm, 113 Gm and 135 Gm collapsible tubes A water soluble stearic acid emulsion having a pH of 4.2 to 4.4 prepared from the formula

Phenylmercuric acetate	Per Cent
Boric acid	0.02
Oxyquinolin benzoate	2.0
.....	0.02
.....	20.0
.....	0.02
.....	5.0
.....	3.0
.....	1.0
Glycerin	5.0
Perfume	0.015
Water sufficient to make	100.00

Packaged with a vaginal applicator or in refill packages containing a tube of cream only

U S trademark 213 756

Koromex Jelly 85 Gm 128 Gm. and 142 Gm. collapsible tubes A water soluble jelly formed from tragacanth and gum acacia having a pH of 4.6 prepared from the formula

Phenylmercuric acetate	Per Cent
.....	0.02
.....	2.0
.....	0.02
.....	0.02
.....	10.0
.....	0.6
.....	2.5
.....	0.015
Water sufficient to make	100.00

Packaged with a Koromex Vaginal Applicator or in refill packages containing a tube of jelly only.

U. S. Trademark 213,756.

Koromex Vaginal Applicator: A transparent plastic tube threaded at the blunt, intravaginal end, to screw onto tubes of Koromex Jelly to permit filling by compression of the tube. The full capacity is 5 cc., the recommended dose.

THE SPECIAL FORMULA CORPORATION

Lygel Vaginal Cream: 85 Gm. collapsible tubes. A white stearic acid cream having a pH of 3.4, prepared from the formula:

	Per Cent
Lactic acid	0.35
Stearic acid	18.00
p-chloro-symm m.—Xylenol	0.10
p-tert. amylphenol	0.10
Cetyl alcohol	4.00
Nacconol	2.00
Sorbitol	6.00
Perfume	0.10
Water sufficient to make	100.00

Packaged with a Lygel Vaginal Applicator or in refill packages containing a tube of cream only.

Lygel Vaginal Jelly: 92 Gm. collapsible tubes. A water soluble jelly having a pH of 3.4 prepared from the formula:

	Per Cent
Lactic acid	0.25
Benzalkonium chloride	0.10
p-chloro-symm m dimethylhydroxybenzene	0.05
p-tert. amylphenol	0.05
Glycerol	15.00
Gum tragacanth and pectin	3.50
Perfume oil	0.10
Water, sufficient to make	100.00

Packaged with a Lygel Vaginal Applicator or in refill packages containing a tube of jelly only.

U. S. patent 1,953,413 (April 3, 1934).

U. S. trademarks 343,141 and 348,042.

Lygel Vaginal Applicator: A transparent plastic syringe threaded to screw onto the tubes of Lygel Vaginal Jelly, to permit filling by compression of the tube. The full capacity is 5 cc., the recommended dose.

U.S. patents 1,918,706; 2,077,176; 2,161,178.

ORTHO PHARMACEUTICAL CORP.

Ortho-Creme: 82.5 Gm. and 123.75 Gm. collapsible tubes. A nonfatty stearic acid cream having a pH of 6, prepared from the formula:

	Per Cent
Stearic acid	24.00
Boric acid	2.00
Ricinoleic acid	0.75
Cetyl alcohol	0.50
Sodium lauryl sulfate	0.28
Triethanolamine	0.25
Glycerin	8.00
Perfume	0.05
Water sufficient to make	100.00

Packaged with an Ortho Vaginal Applicator or in refill packages containing a tube of cream only

U S patent 2,330,846 (Oct 3 1943) expires 1960) U S trademark 390,141

Ortho Gynol Vaginal Jelly 90 Gm and 150 Gm. collapsible tubes. A water soluble jelly formed from tragacanth and acacia having a pH of 4.5 prepared from the formula

	Per Cent
Boric acid	3.00
Ricinoleic acid	0.75
Oxyquinoline sulfate	0.025
Propyl p-hydroxybenzoate	0.05
Glycerin	5.00
Acacia	2.00
Tragacanth	3.00
Perfume	0.025
Water sufficient to make	100.00

The concentration of the active ingredients is 50.05 mg. per cc. of penetration

all pack

U S trademark 298,222

Ortho Vaginal Applicator A transparent plastic syringe threaded at the blunt intravaginal end, to screw onto the tubes of Ortho Gynol Vaginal Jelly or Ortho-Creme to permit filling by compression of the tube. The full capacity is 5 cc., the recommended dose.

U S trademark 394,998

JULIUS SCHMID INC.

Ramses Vaginal Jelly 92 Gm and 143 Gm collapsible tubes. A water soluble jelly formed from carboxymethylcellulose and glycerin having a pH of 5 prepared from the formula

	Per Cent
Dodecaethylene glycol monolaurate	5.00
Boric acid	1.00
Alcohol	5.00
Carboxymethylcellulose	2.50
Glycerin	7.00
Butyl parahydroxybenzoate	0.02
Perfume	0.01
Water sufficient to make	100.00

Packaged with a Ramses Vaginal Applicator or in refill packages containing a tube of jelly only

U S trademark 306,696

Ramses Vaginal Applicator: A transparent plastic tube threaded at the blunt intravaginal end to screw onto the tubes of Ramses Jelly to permit filling by compression. A plastic cylinder fitted inside the tube permits the operator to expel the jelly. The full capacity is 5 cc., the recommended dose.

U. S. patents 1,918,706 and 2,077,176.

WHITTAKER LABORATORIES, INC.

Cooper Creme: 75 Gm. collapsible tubes. A white, non-greasy, water miscible stearate cream having a pH of 7.3 prepared from the formula:

	Per Cent
Stearic acid	23.04
Trioxymethylene, U. S. P.	0.04
Diocetyl sodium sulfo succinate	0.50
Sodium oleate	0.67
.....	7.91
.....	2.34
.....	100.00

Packaged with a Cooper Creme Dosimeter or in refill packages containing a tube of cream only.

Cooper Creme Dosimeter: A transparent plastic tube, threaded at the blunt intravaginal end to screw onto the tubes of Cooper Creme to permit filling by compression of the tube. The full capacity of the dosimeter is 10 cc.

Capsules and Suppositories

Actions and Uses—Capsules and suppositories provide a convenient method for introducing obstructive and spermicidal material into the vagina with the advantage of freedom from the need of apparatus. The solid material introduced must be converted to a jelly or liquid form in order to cover the requisite area; hence prompt liquefaction is important. For some suppositories this results from a melting point below the temperature of the body. For others the active material is enclosed in a gelatinous shell which melts or opens when exposed to body temperature and moisture. The time required should be under ten minutes, and the users should be instructed to allow more time than this, at least fifteen minutes, to elapse before intercourse. A douche should not be taken less than six hours after ejaculation.

To insure further protection, physicians should advise the concurrent use of an occlusive device such as a diaphragm, and should stress the fact that suppositories or capsules used alone are less effective.

EATON LABORATORIES

Lotophyn Suppositories (Vaginal): Suppositories are hermetically sealed in foil. They consist of self-emulsifying, water-soluble, low-melting mass prepared from the formula:

	Per Cent
Phenylmercuric acetate	0 05
Glyceryl mono-laurate	10 00
Tween 61 (Sorbitan monoacetatehydroxy polyoxyethyl ene ether	89 95

Dosage.—One suppository containing 3 Gm

U S. trademark 417,240.

PERNOY, INC.

Pernox Vaginal Capsules: A soft gelatin capsule containing a low melting mass prepared from the formula.

	0 045 Gm.
	1 830 Gm.
	0 185 Gm.
	0 045 Gm.
	0 220 Gm.
Anhydrous lanolin	1 100 Gm.
Liquid petrolatum	0 770 Gm.
Yellow petrolatum	0 110 Gm.
Tragacanth	0 214 Gm.

Dosage.—One capsule, containing 4 5 Gm.

SPECIAL FORMULA CORPORATION

Lygenes Vaginal Suppositories: 2.25 Gm A vaginal suppository with an oil of theobroma base prepared from the formula.

	Per Cent
Boric acid	0 10
Zinc sulfocarbolate	0 50
Hydroxyquinoline benzoate	0 30
p-Chloro-symm. m-dimethyl hydroxybenzene	0 05
p-tert. amylhydroxy benzene	0 05
Beeswax, white	5 00
Corn starch	9 00
Perfume	0 20
Cocoa butter	84 80

Actions and Uses.—See article on Contraceptive Capsules and Suppositories

Dosage.—One suppository, containing 2.25 Gm.

Diagnostic Aids

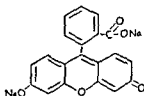
In this chapter are assembled various drugs whose use internally or externally helps to reveal the anatomical evidences of disease or whose excretion from the body furnishes a physiological test of renal or hepatic function. The list includes barium and iodine compounds used as contrast media in roentgenography, certain dyes used in testing the functional capacity of the kidneys and liver, and antigenic preparations not classed with Agents Used in Allergy or Serums and Vaccines.

Allergenic extracts used for diagnosis are included in the chapter on Agents Used in Allergy. Toxins used in immunity tests are described in the chapter on Serums and Vaccines.

EXTERNAL

FLUORESCEIN SODIUM-U. S. P.—"When dried to constant weight at 105 C., contains not less than 98.5 per cent of $C_{20}H_{10}O_5Na$." *U. S. P.*

Fluorescein is formed by condensing resorcinol with phthalic anhydride. Fluorescein sodium may be represented by the following structural formula:



For description and standards see the U. S. Pharmacopeia under Fluorescein Sodium.

Fluorescein is closely related to phenolphthalein from which it differs in structure by the presence of an oxygen bridge linking the phenol nuclei in their ortho positions. In common with the phthaleins, it forms salts with alkali whereby a rearrangement takes place and the quinolyl group is formed. Fluorescein is brominated easily to form the beautiful dye eosin, the tetrabromo derivative.

Actions and Uses—The soluble sodium salt of fluorescein (fluorescein 2 Gm, sodium bicarbonate 3 Gm, water to make 100 cc.) has been used for the diagnosis of corneal lesions and

the detection of minute foreign bodies embedded in the cornea. While a weak solution of fluorescein will not stain the normal cornea, ulcers or parts deprived of epithelium will become green and remain so for a time, foreign bodies will appear surrounded by a green ring, loss of substance in the conjunctiva is indicated by a yellow hue. Fluorescein also reveals defects or disease of the endothelium of the cornea, producing a deep coloration of the diseased area.

MEACK & Co, INC

Fluorescein (Powder)

TRICHINELLA EXTRACT — Trichinella extract is diluted saline extraction of clean Trichinella larvae prepared by artificial digestion of muscles of heavily infested experimental animals. The extract is adjusted to neutrality and sterilized by filtration.

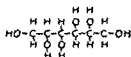
ELI LILLY AND COMPANY

Trichinella Extract Two 1 cc vials, one vial of Trichinella Extract 1:10,000 dilution in isotonic solution of sodium chloride, and one control vial of isotonic solution of sodium chloride used as extracting fluid. Both extract and control solution contain Merthiolate 1:20,000 as a preservative.

INTERNAL

Agents Used for Kidney Function Tests

A hexahy-
formula of



For tests and standards see Section B

Actions and Uses — Mannitol is a hexahydric alcohol which is filtered at the glomeruli but is neither reabsorbed nor excreted by the tubules. Mannitol may be used to measure glomerular filtration. The normal values for the glomerular filtration rate are 131 ± 21.5 cc. per minute for men and 117 ± 15.6 cc. per minute for women. These values are corrected to a standard sur-

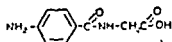
face area of 1.73 square meters. In the presence of renal disease in which the glomeruli are damaged, values lower than normal are found. The validity of results of clearances with mannitol is questioned by some observers.

Dosage.—Mannitol is administered as a sterile 25 per cent solution by venoclysis. The concentration of mannitol is determined in milligrams per cubic centimeter of blood plasma. The urine formed during a definite period is collected, and the mannitol excreted is calculated in milligrams per minute. The glomerular filtration rate in cubic centimeters per minute is calculated from these two values and is equivalent to the number of cubic centimeters that must have been filtered at the glomerulus to supply the amount of mannitol excreted in the urine per minute.

SHARP & DOHME, INC.

Solution Mannitol: 50 cc. ampuls. Each ampul contains 12.5 Gm mannitol.

PARA-AMINOHIPPURIC ACID.—4-aminobenzoylglycine.—The N-acetic acid amide of para-aminobenzoic acid.—The structural formula of para-aminohippuric acid may be represented as follows:



For tests and standards, see Section B.

Actions and Uses.—Sodium para-aminohippurate is excreted by the tubular epithelium of the kidneys in addition to being filtered by the glomerulus. It may be used to measure the effective renal capacity

renal plasma
100 cc.) are
this compound
circulation.
135.9 cc. per
women. This
amide com-
ents used in

the test.

the functional capacity of the tubular excretory
in
er

minute.

Method of Application.—To Determine Effective Renal Plasma Flow: Sterile solution of sodium para-aminohippurate is injected intravenously in a volume sufficient to produce approximately 2 mg. of para-aminohippurate per 100 cc. of blood

plasma. At this plasma level all the para aminohippurate in the blood that passes through the kidney is removed and appears in the urine. The urine formed during a definite but relatively short period is collected and the average amount of para amino hippurate eliminated is calculated in milligrams per minute. This value divided by the para aminohippurate content of the plasma in milligrams per cubic centimeter is equivalent to the number of cubic centimeters of plasma per minute that must have passed through the kidneys (effective renal plasma flow)

To Determine Tubular Excretory Mass Sterile solution of sodium para aminohippurate is injected intravenously in a volume sufficient to saturate the capacity of the tubular cells to excrete para aminohippurate (above 60 mg per 100 cc of plasma), and the para aminohippurate content of the plasma is determined in milligrams per cubic centimeter. The amount excreted in the urine is determined in milligrams per minute this value including both glomerular filtration and tubular excretion. The glomerular filtration rate using mannitol a compound that is filtered only through the glomerulus is determined in cubic centimeters per minute (see description of Sterile Solution of Mannitol). From the glomerular filtration rate and the para aminohippurate content per cubic centimeter of plasma is calculated the amount of para aminohippurate that was filtered through the glomeruli in one minute ($\text{cc/min} \times \text{mg/cc.}$) Then the total number of milligrams excreted in the urine per minute minus that amount filtered through the glomeruli per minute equals the amount of para aminohippurate in milligrams per minute excreted by the tubules (tubular excretory mass)

SHARP & DOHME, INC.

Solution of Sodium Para Aminohippurate 50 cc. ampuls
Each 50 cc. contains 10 Gm of sodium para aminohippurate, buffered to pH 7.0 with citric acid

Para Aminohippuric Acid (Reagent) 2 Gm vials For use in the preparation of standard solutions

PHENOSULFONPHTHALEIN—See section on Phenol phthalein dyes

Benzoic Acid Derivatives

SODIUM BENZOATE U S P—When dried at 100 C. for 4 hours contains not less than 99 per cent of $\text{C}_6\text{H}_5\text{COONa}$.
U S P The structural formula may be represented as follows



For standards see the U S Pharmacopeia under Sodium Benzoate

Actions and Uses.—The intravenous use of sodium benzoate as a liver function test was suggested by Quick and his co-workers in 1938 (Quick, A. J.; Ottenstein, H. N., and Weltcheck, Herbert: *Proc. Soc. Exper. Biol. & Med.* 38:77 [Feb] 1938) to overcome the disadvantages associated with its oral administration. In the presence of normal liver function in man benzoate is converted to hippuric acid and excreted in the urine. Clinical signs are evident.

The test is contraindicated in the presence of renal disease, because here the hippuric acid is but partially eliminated.

Dosage.—The bladder is emptied before administration of the drug. Inject *slowly*, intravenously, 20 cc. of sodium benzoate solution containing 1.77 Gm. of the salt (equivalent to 1.5 Gm. of benzoic acid), using not less than five minutes for the injection. Exactly one hour after the injection a complete urine specimen is collected and the amount of hippuric acid determined. (Quick, A. J.: *Am. J.*

excrete at least 1 Gm. of n. of benzoic acid) within 2 hours after intravenous injection.

GEORGE A. BREON & COMPANY, INC.

Solution Sodium Benzoate: 1.77 Gm. (equivalent to 1.5 Gm. benzoic acid) in 20 cc. ampuls

Barium Sulfate

BARIUM SULFATE—U. S. P.—Sklabaryt (MERCK).— BaSO_4 —For description and standards see the U. S. Pharmacopeia under Barium Sulfate.

Actions, Uses and Dosage.—Barium sulfate for roentgen examination, being freed from soluble barium and other salts, passes unchanged through the digestive tract and because of this is used in taking roentgenograms of the stomach and of the intestines.

For Roentgen Examination of the Stomach.—A barium sulfate suspension usually is made to contain 300 Gm. of the sulfate in 400 cc. of water, but the amount of water may vary according to the thickness of mixture desired.

For Roentgen Examination of the Colon.—A barium sulfate suspension is made to contain 750 Gm. of the sulfate in 1,500 cc. of water.

The patient should be prepared by the administration of 1 ounce of castor oil the night before the examination and of a plain water or saline enema two hours before the procedure is performed.

The suspension warmed to body temperature is injected into the rectum by enema tube from a height of 90 to 180 cm.

Caution—When Barium Sulfate is prescribed, the title should always be written out in full to avoid confusion with the poisonous barium sulfide or sulfate U S P

MALLINCKRODT CHEMICAL WORKS

Barium Sulfate for X-Ray Diagnosis Bulk.

MERCK & Co., Inc.

Barium Sulfate for X Ray Diagnosis Bulk.

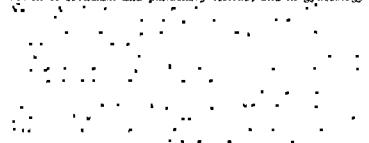
Skibaryt for Oral Administration A mixture of barium sulfate, 80 to 83 per cent, sugar, tragacanth, vanilla, cinnamon and cacao.

Skibaryt for Rectal Administration A mixture of barium sulfate U S P., 90 per cent, sugar and tragacanth.

U S. trademark 155,022

Iodized Oils

Iodized oils are injected as contrast mediums in roentgen diagnosis, especially of tumors of the spinal cord, in the localization of bronchial and pulmonary lesions, and in gynecology



advantages of other measures. The following cautions should be especially borne in mind

"1 Oils that have aged and darkened beyond their original color should never be used.

"2 Subarachnoid injections should be avoided, at least until all other means of diagnosis have been exhausted.

"3. Intratracheal and intrapleural injections should be avoided in tuberculosis of the respiratory organs and also when restriction of respiratory area would be contraindicated.

"4 The injection pressure should be carefully controlled, so as not to lacerate the tissues.

"5 Intra uterine injections should be made only under fluoroscopic observations

"6 Iodized oil should not be used for renal pyelography except in the form of emulsion and the injection should be stopped if pain is felt.

"7 Intravascular injections with iodized oil appear too dangerous, the use of emulsions for this purpose requires further

study." (D. C. ... Council
99: 1946
further c
oils.)

8. When the so-called per-nasal method of injecting the oil into the larynx is employed, it should be remembered that in the injection of the local anesthetic required for this procedure, the risk of intoxication from the anesthetic is greatly enhanced as the absorptive surface is increased.

IODIZED OIL-U. S. P.—Lipiodol, 40% Iodine (FOUGERA).—Lipiodol 40% Iodine Radiologique Descendant (FOUGERA).—"An iodine addition product of vegetable oils, containing not less than 38 per cent and not more than 42 per cent of organically combined iodine (I)." U. S. P.

For description and standards see the U. S. Pharmacopeia under Iodized Oil.

Actions and Uses.—Iodized oil is used as a substitute for inorganic iodides; and as a contrast medium in roentgenography. See general article, Iodized Oils. In subarachnoid injection for roentgen examination, iodized oil is used for the recognition of intradural tumors.

Dosage.—From 1 cc. to 5 cc. or more according to the uses to which it is to be put.

E. FOUGERA & COMPANY, INC.

Solution Lipiodol in Oil (40% Iodine): 1 cc., 2 cc., 3 cc. and 5 cc. ampuls and 20 cc. neoprene-capped flask. An iodine addition product of poppy seed oil.

Solution Lipiodol in Oil (40% Iodine Radiologique Descendant): 5 cc. flasks.

U. S. trademark 196,499.

IODOBRASSID ...
side. — ...
contains 4 ...
represented as follows:



For tests and standards, see Section B.

Actions and Uses—Iodobrassid is used as a substitute for the inorganic iodides and as a contrast medium for roentgenologic work. See general article, Iodized Oils.

For diagnostic work, from 5 to 20 cc. of iodobrassid, as determined by the extent of the field to be investigated.

CIBA PHARMACEUTICAL PRODUCTS, INC.

Solution Lipiodine in Oil (Diagnostic): 10 cc. bottle. A 60 per cent solution of iodobrassicid in sesame oil

U. S. patent 1,024,171 (April 23, 1912; expired).

U. S. trademark 81,554.

iodine (0.11 Gm. of iodine per cc.) in organic combination

For tests and standards, see Section B

Actions and Uses—This iodized preparation is used for recognition of intradural tumors when it is desired to employ a contrast medium of lesser density than that of the spinal fluid.

Dosage—From 1 to 2 cc., previously brought, with the syringe, to a temperature of 40 C.

E. FOUGERA & COMPANY, INC.

Solution Lipiodol in Oil (Radiologique Ascendant): 5 cc. flasks

U. S. trademark 196,499

Water-Soluble Organic Iodine Compounds for Roentgenography

Satisfactory roentgenograms of the urinary tract may be secured by the intravenous injection of soluble iodine compounds of low toxicity, which are rapidly excreted by the urine. Several organic compounds are now available for this use. Sodium iodide, in the necessary dose, is too toxic for intravenous injection. The organic compounds may also be used for ureteral retrograde pyelography.

The intravenous urography is now generally accepted that

coughing, "tight feeling", or choking sensation, and cyanosis
 or varying periods of time

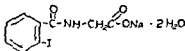
Any history of allergy

there is reason to suspect

that a reaction may occur a small initial dose may be given first. In any event, epinephrine hydrochloride 1:1,000 should be available when the injection is made. The intravenous use of the drug is contraindicated in patients with severe liver disorders, nephritis and severe uremia, and it should be used with caution in cases of active tuberculosis and of hyperthyroidism. Excretory urography should not be used routinely in all patients. Further, this method may have to be checked with retrograde pyelography, and either or both methods closely correlated with the clinical findings. Injection of the medium into the kidney pelvis is most accurately gauged by using a manometer, but lacking this instrument gravity or a syringe may be employed

varicose veins.

HIPPURAN (MALLINCKRODT).—Sodium *ortho*-iodohippurate dihydrate. This compound contains 34.95 per cent of iodine, or 38.8 per cent when calculated to the dried substance. Its structural formula may be represented as follows:



For tests and standards, see Section B.

Actions and Uses.—Sodium *ortho*-iodohippurate is proposed for use as a radiopaque agent for intravenous, oral or retrograde

ing rarely. Fasting and dehydration of patients prior to administration of the drug are usually employed. Pressure over the bladder region is employed by some clinicians; this is released immediately before the first exposure and is replaced until the next. Ordinarily the first film is exposed about ten minutes after injection and two subsequent pictures are taken at fifteen or twenty minute intervals. In case excretion is delayed, later exposure may be necessary.

Results with oral administration of the drug are less satisfactory but a sufficiently high percentage of successful pictures appear to be obtained to make this method worthy of trial in occasional cases in which intravenous or retrograde urography

is not feasible. The somewhat objectionable taste of the compound usually does not militate against its ingestion. Toxic effects after oral administration have not been reported. Pictures are taken 60, 90, 120 and 150 minutes after oral administration. The use of moderate compression over the bladder region is recommended in the intervals between exposures. While the iodine in sodium *ortho*-iodohippurate is firmly bound, the compound should nevertheless be used with caution in patients with hyperthyroidism and tuberculosis. The intravenous use of the drug is contraindicated in severe liver disorders, nephritis and uremia. In suspected cases preliminary hepatic and renal function tests should be employed.

Satisfactory visualization has been reported with this preparation when employed by the retrograde method for urethrograms, cystograms or pyelograms. There is said to be little or no tissue irritation with effective concentrations.

Dosage—For intravenous use, 25 cc. of a solution containing 12 Gm. of sodium *ortho*-iodohippurate previously warmed to body temperature is injected into the cubital vein. Young children are given proportionately smaller doses. For oral use 12 Gm. of sodium *ortho*-iodohippurate is dissolved in 75 cc. of simple syrup. For children, 10 Gm. is employed. For retrograde use sodium *ortho*-iodohippurate is employed in 15 to 20 per cent solution for pyelography or 3 to 5 per cent solution for cystography. The solution may be made either by diluting the ampule solution with sterile distilled water or by dissolving the crystals in distilled water, filtering and sterilizing by heat.

MALLINCKRODT CHEMICAL WORKS

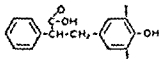
Hippuran (Powder): Bulk.

Hippuran (Crystals): 12 Gm., 100 Gm. and 500 Gm. bottles.

Solution Hippuran. 12 Gm., 25 cc. ampuls.

U. S. patent 2,155,474 (Nov. 1, 1938, expires 1955) U. S. trademark 114,377.

IDOALPHONIC ACID—**Priodax (SCHERING)**— β (4-hydroxy-3,5-diiodophenyl)- α -phenylpropionic acid.—Iodoalphonic acid contains 51.38 per cent of iodine. Its structural formula may be represented as follows:



For tests and standards, see Section B.

Actions and Uses—Iodoalphonic acid is used as a medium for cholecystography. It is claimed to cause less nausea, vomiting and diarrhea than tetraiodophenolphthalein. The drug is excreted primarily through the kidneys.

Iodoalphonic acid is contraindicated in acute nephritis.

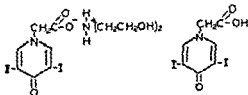
uremia and acute disorders of the gastrointestinal tract. Side effects that may be encountered occasionally include pain on urination, nausea, vomiting, diarrhea, griping, headache, sensation of burning in the esophagus, generalized itching, dryness of the mouth, general weakness and flatulence.

Dosage.—The average adult dose is 3 Gm., although more may be given. The patient swallows the drug during or after a light fat-free meal in the late afternoon. Nothing is then eaten until the roentgenologic examination is completed the next morning.

SCHERING CORPORATION

Tablets Priodax: 0.5 Gm.

IODOPYRACET COMPOUND SOLUTION.—**Dio-drast Compound Solution (WINTHROP-STEARN'S).**—An aqueous solution containing approximately 40.5 per cent of the diethanolamine salt of 3,5-diiodo-4-pyridone-N-acetic acid and approximately 9.5 per cent of 3,5-di-iodo-4-pyridone-N-acetic acid. Iodopyracet compound solution contains about 25 per cent (W/V) of iodine in organic combination. The structural formulas of the diethanol amine salt of 3,5-di-iodo-4-pyridone-N-acetic acid and 3,5-di-iodo-4-pyridone-N-acetic acid may be represented, respectively, as follows:



Iodopyracet compound solution is prepared by neutralizing 3,5-diiodo-4-pyridone-N-acetic acid in water with appropriate quantities of diethanolamine and diethylamine. The salts formed are soluble in water and are not isolated.

For tests and standards, see Section B.

Actions and Uses.—Iodopyracet compound solution is used for roentgenographic examination of the gastrointestinal tract.

It is particularly useful in the examination of the small intestine, pervis through large intestine, and in a small volume of solution particularly for injection of obese subjects or for patients who cannot or will not cooperate in the preliminary preparation for excretion urography with iodopyracet injection. Roentgenographic examination taken at 5, 15 and 45 minute intervals.

Delayed excretion of iodopyracet compound solution is not a contraindication to its use in excretion urography. Iodopyracet compound solution is not a contraindication to its use in excretion urography.

Dosage

For excretion urography, iodopyracet compound

solution is administered intravenously in sterile aqueous solution, the average dose for adults being 20 cc. Iodopyracet compound solution may be employed without dilution for retrograde cholangiography. For economy

concentration
grams; this
in this indiv
retrograde es

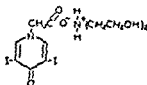
WINTHROP-STEARNs, INC.

Compound Solution Diodrast—20 cc. ampuls

U S patent 1,993,039 (March 5, 1935, expired 1952) U S trademark 312,451

IODOPYRACET CONCENTRATED SOLUTION.—

Diodrast Concentrated Solution (WINTHROP STEARNs) —An aqueous solution containing 70 per cent of the diethanolamine salt of 3,5-diiodo-4-pyridone-N-acetic acid, the structural formula of which may be represented as shown below. Iodopyracet concentrated solution contains about 44 per cent (W/V) of iodine in organic combination.



Iodopyracet concentrated solution is prepared by neutralizing 3,5-diiodo-4-pyridone-N-acetic acid in water with an equimolecular quantity of diethanolamine. The salt formed is soluble in water and is not isolated.

For tests and standards, see Section B.

Actions and Uses —Iodopyracet concentrated solution is employed for use in a special diagnostic procedure for visualization of the heart, the ascending and descending aorta and branches, the superior vena cava, the pulmonary artery and branches, the coronary arteries and other structures of the heart and mediastinum. It has also been used for cholangiography by injection of the material into the common bile duct. The technic in using this agent is relatively complicated and requires accurate timing and teamwork between the physician, the patient and the roentgenologist. The method consists in injecting the substance into the blood and taking roentgenograms simultaneously with the concentration of the opaque material in the cardiopulmonary

system. In addition a preliminary examination of the chest with the x-rays is necessary to obtain data for contrast medium. At times it is necessary to do this for accuracy. The contraindications are nephritis and hyperthyroidism. It should be given cautiously in the presence of heart disease and circulatory failure, never in those patients with severe heart failure. Preliminary renal function test should be given. The patient should not be given the drug if the stomach should be empty. It should be given after vomiting, sense of intense thirst, transient pain at the site of injection, etc. Delayed reaction, etc.

there

This

technic can be mastered by experienced workers who have the proper facilities, although it might be dangerous in the hands of persons who are inexperienced or by those who use the technic in a casual manner. In skilled hands untoward reactions are comparatively few. It is claimed by the manufacturer that this agent is sufficiently stable to permit boiling for a short time if a question of sterility should arise, although the product is marketed in sterile form.

Dose: 15 cc. to 100 cc. depending on the size of the patient and the degree of the disease. It should be given after vomiting, sense of intense thirst, transient pain at the site of injection, etc. Delayed reaction, etc.

Indications: For the diagnosis of pulmonary congestion, the size of the heart, the size of the certain pulmonary congestion.

present warm solution to body temperature before using.

For cholangiography the amount of iodopyracet concentrated solution varies within wide limits; as little as 15 cc. and as much as 100 cc. has been required by direct injection into the common bile duct.

For description and standards see The U. S. Pharmacopeia under Iodopyracet Injection and the additional tests, as far as they apply, under Iodopyracet Compound Solution-N. N. R. (Since Iodopyracet Injection-U. S. P. is only about half the strength of Iodopyracet Compound Solution, the quantities given in the U. S. P. standards must be multiplied by two.)

WINTHROP-STEARNs, INC.

Concentrated Solution Diodrast 70% W/V: 50 cc. ampul.

IODOPYRACET

(WINTHROP STEARNS) -

of 3,5 diiodo 4 pyridone

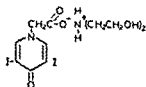
 $\text{NH}(\text{CH}_2\text{CH}_2\text{OH})_2$, ci

Gm and not more than

diiodo-4 pyridone-N ace

not less than 61.5 per c

iodine" U S P The structural formula may be represented as follows



Iodopyracet injection is prepared by neutralizing 3,5 diiodo-4-pyridone N acetic acid in water with an equimolecular quantity of diethanolamine. The salt formed is very soluble in water and is not isolated.

For description and standards see The U S Pharmacopeia under Iodopyracet Injection.

Actions and Uses—Iodopyracet is used as a contrast agent for intravenous urography. Local reactions about the site of injection are absent or very mild, systemic reactions occur occasionally. The latter consist chiefly of flushing of the skin with a sense of warmth, less often transient nausea vomiting, erythematous eruptions, respiratory distress and cyanosis. These side effects usually subside within a few minutes to an hour or so without special therapy, but the skin eruptions may rarely persist

(thirty minutes or more). A safe routine is to take roentgenograms at 5, 15 and 45 minutes after injection of the drug. Pressure over the bladder is employed by some clinicians, this

thyroidism. Preliminary renal and hepatic function tests are advisable in suspected cases. Caution should be exercised in cases

0.35 Gm. Twenty cc. of a solution containing 7 Gm. of iodopyracet, previously warmed to body temperature, is injected slowly, usually into the cubital veins. Children are given correspondingly smaller doses. It may be administered intramuscularly or subcutaneously in infants, children, and adults with inaccessible or

may be used if needed.

WINTHROP-STEARNs, INC.

Solution Diodrast 35%, W/V: 10 cc., 20 cc. and 30 cc. ampuls

U. S. patent 1,993,039 (March 5, 1935; expires 1952). U. S. trademark 312,451

METHIODAL SODIUM—Skiodan (WINTHROP-STEARNs).—The sodium salt of monoiodomethanesulfonic acid $\text{CH}_2\text{I}.\text{SO}_3\text{Na}$.—Methiodal sodium contains 52 per cent iodine.

For tests and standards, see Section B.

tion or by direct injection into the renal pelvis through a ureteral catheter. It exerts a diuretic action, most marked during the first half hour after intravenous injection. Excretion studies show that within a few minutes after intravenous injection the concentration of methiodal sodium in the urine reaches a maximum of from 4 to 6 per cent (corresponding to from 2 to 3 per cent of iodine). Usually, 75 per cent is eliminated in three hours, more than 90 per cent in ten hours, and the remainder within about twenty-four hours.

Dosage.—For intravenous urography, methiodal sodium is administered in sterile aqueous solution (from 20 to 40 Gm. in 100 cc.), the average dosage for adults being about 2 Gm. for each 15 pounds of body weight; for retrograde pyelography an aqueous solution of methiodal sodium (from 10 to 20 Gm. in 100 cc.) is injected through a ureteral catheter in the renal

pelvis Cystograms may be made with 3 to 5 per cent solutions Aqueous solutions of methiodal sodium should be kept protected from light, they can be kept for a considerable time without impairment but should be reesterilized before use.

For retrograde pyelography 10 to 20 Gm in 100 cc. methiodal sodium solution is used In thin patients a 10 per cent concentration often suffices The injection is made in the customary manner through the ureteral catheter In cases of suspected stone some urologists prefer a 5 per cent or 6 per cent solution for thin persons to assure satisfactory contrast In the preparation of methiodal sodium solutions for retrograde pyelography, distilled water should be used The solution should be sterilized by boiling or autoclaving

On the day before the intravenous injection of methiodal sodium the patient is given a soft diet, with a cleansing enema in the evening During the night the fluid intake is restricted as much as possible

WINTHROP-STEARNs INC.

Skiodan (Powder) 20 Gm bottles

Solution Skiodan Sodium 20% 50 cc bottles of a sterile solution of methiodal sodium

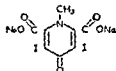
Solution Skiodan Sodium 40% 50 cc. and 100 cc bottles of a sterile solution of methiodal sodium

Tablets Skiodan 1 Gm for retrograde pyelography

U S patent 1,842,626 (Jan. 26 1932 exp res 1949) U S. trademark 283 045

SODIUM IODOMETHAMATE (SCHERING) — Neo Iodo 4-pyridone 2,6-diiodo-5-diiodochelidamic acid Sodium iodomethamate contains 51.5 per cent iodine

The structural formula may be represented as follows



For tests and standards see Section B

Actions and Uses—Sodium iodomethamate is used as a contrast medium in intravenous urography and retrograde pyelography Clinical reports indicate that systemic reactions occur uncommonly and are usually mild and fleeting In some cases there is more or less severe pain in the arm radiating to the shoulder, usually this disappears on completion of the injection but in a small percentage of cases it may persist for a variable period The pain may usually be relieved by local applications of heat and the administration of an analgesic when necessary

Fluid intake should be restricted for about twelve hours prior to the examination. If only anatomic information is desired, it is usually sufficient to take a single roentgenogram from ten to twenty minutes after injection. In other cases, a series of roentgenograms are taken at intervals of five, fifteen and thirty minutes after injection. It is advisable to take a film over the urinary bladder area when making the roentgenogram thirty minutes after the injection. If the first plates show that but little of the drug has been excreted, it is presumed that the kidneys are functioning poorly, and several hours should be allowed to elapse, during which plates should be made at intervals. Impairment of renal function will allow but poor concentration of the drug; many hours are then required for its excretion. The intravenous use of the drug is contraindicated in patients with severe liver disorders, nephritis and severe uremia and it should

Dosage.—Twenty cc. of solution containing 15 Gm. of sodium iodomethamate previously warmed to body temperature is injected into the cubital vein. Children are given correspondingly smaller doses.

SCHERING CORPORATION

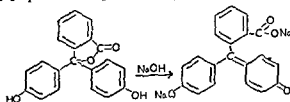
Solution Neo-Iopax: 10 cc. and 20 cc. ampuls. Each 1 cc. contains 0.75 Gm. of sodium iodomethamate in sterile distilled water.

Solution Neo-Iopax: 10 cc. and 20 cc. ampuls. Each 1 cc. contains sodium iodomethamate 0.5 Gm., dissolved in sterile distilled water.

U. S. patent 1,919,417 (July 25, 1933; expires 1950). U. S. trademark 297,925.

Phenolphthalein Dyes

Phenolphthalein—long used by chemists as an indicator before its therapeutic properties were discovered—is a condensation product of phthalic anhydride and phenol. In neutral and acid

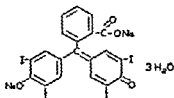


ence of a quinonoid group whereby the red color is produced. This reaction is also characteristic of other members of the

series Phenolsulfonphthalein—also used as an indicator—contains an SO_2 group in place of the CO group in the phthalic anhydride nucleus. In phenoltetrachlorophthalein and phenoltetraiodophthalein the four hydrogen atoms in the benzene ring belonging to the phthalic acid nucleus have been replaced by chlorine and iodine, respectively, in tetrabromophenolphthalein, two bromine atoms are on each phenol group.

Actions and Uses—All of the compounds of the phenolphthalein type are used in medicine as diagnostic agents except phenolphthalein itself. Phenolphthalein is used for its cathartic action. Phenolsulfonphthalein and phenoltetrachlorophthalein are used because they pass unchanged through the body and at the same time have the property of intense color formation when the excretions are collected and alkalinized. Bromosulfaphthalein is used in a somewhat analogous way but instead of determining the amount excreted by the bile the amount (not excreted) in the blood gives an index of liver function. Tetrabromophenolphthalein and tetraiodophenolphthalein—which are employed in the form of the sodium salts—are used as carriers of bromine or iodine, they appear in the gallbladder in sufficient concentration to permit the heavy halogen atoms to cast a shadow to the roentgen rays.

IODOPHTHALEIN SODIUM—U. S. P.—Iodeikon (MALLINCKRODT)—Tetraiodophenolphthalein Sodium—The disodium salt of tetraiodophenolphthalein. It contains not less than 85 per cent of tetraiodophenolphthalein. The separated tetraiodophenolphthalein contains not less than 60 per cent and not more than 63 per cent of iodine (I).—U. S. P. The structural formula may be represented as follows:



For description and standards see the U. S. Pharmacopeia under Iodophthalein Sodium.

Actions and Uses—Iodophthalein sodium is used for the roentgenologic examination of the gallbladder. Following the intravenous injection or, if decomposition is avoided, the oral administration, the substance appears in the normal gallbladder in sufficient concentration to cast a shadow to the roentgen rays. After injection, a few of the patients may have unpleasant sensations, such as dizziness, nausea, various body pains and fall in blood pressure. The transitory fall in blood pressure may be relieved by the administration of from 0.5 to 1 cc. of epinephrine hydrochloride solution (1 in 1000) intramuscularly. Iodophthalein sodium is useful as a diagnostic agent, but workers

are cautioned as to the selection of types of cases in which it is indicated and its possible toxicity in large doses. Myocardial insufficiency and uremia are considered contraindications, and jaundice enjoins caution.

Dosage.—To visualize the gallbladder in a patient weighing between 52 and 73 Kg. (115 to 160 lb.), 3 Gm. of iodophthalein sodium is dissolved in 24 cc., or 3.5 Gm. of iodophthalein sodium is dissolved in 28 cc. of freshly distilled water; the solution is then sterilized by heating the container in boiling water for twenty minutes. For patients weighing over 73 Kg. pounds the

tients weighing
to be reduced.
doses, one-half
travasation, in
be given at or

before morning meal time but no food should be given until after the first roentgenogram is taken, usually 4 hours after the injection. A fat meal is then given and a second roentgenogram taken one hour after the meal and, if desired a third 3 hours after the meal, to determine the rapidity and characteristics of emptying. Water by mouth is allowed at all times and the evening meal is allowed as usual.

Iodophthalein sodium may be administered orally: 4 Gm. in the form of plain gelatin capsules (8 capsules of 0.5 Gm. each), or dissolved in 30 cc. of distilled water and added to 120 to 240 cc. of grape juice . . . meal, which should . . . aqueous solution of . . . old). Keratin coated . . . are then taken the . . . Meticulous roentgen

EASTMAN KODAK COMPANY

Tetraiodophenolphthalein Sodium (*Powder*): Bulk.

MALLINCKRODT CHEMICAL WORKS

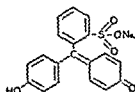
Iodeikon (*Powder*): Bulk.

Iodeikon Sodium: 3.5 Gm. ampuls.

MERCK & Co., INC.

Iodophthalein Sodium (*Powder*): 35 Gm., 25 Gm., 100 Gm. and 500 Gm. bottles.

PHENOLSULFONPHTHALEIN-U. S. P.—Phenol Red.
The structural formula may be represented as follows:



For description and standards see the U. S. Pharmacopeia under Phenolsulfonphthalein and Phenolsulfonphthalein Injection.

Intact in the urine after intramuscular injection of 6 mg. of dye is diminished after intramuscular injection.

Dosage—One cc. of a sterile solution, containing 6 mg. of phenolsulfonphthalein.

HYNSON, WESTCOTT & DUNNING, INC.

Phenolsulfonphthalein (Powder): Bulk.

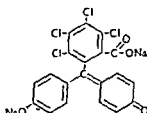
Solution Phenolsulfonphthalein: 1 cc. ampuls Each 1 cc.

of solution contains 6 mg. of phenolsulfonphthalein in the form of the monosodium salt.

NATIONAL ANILINE DIVISION, ALLIED CHEMICAL & DYE CORPORATION

Phenolsulfonphthalein (Powder): Bulk.

PHENOLTETRACHLOROPHTHALEIN.—A dibasic dye formed by the condensation of phenol and tetrachlorophthalic acid or its anhydride. The structural formula may be represented as follows:



For tests and standards, see Section B.

Actions and Uses.—Phenoltetrachlorophthalein has been used for the determination of the functional activity of the liver. It can be used, in the form of the sodium salt, intravenously; it should not be given subcutaneously or intramuscularly. It has been proposed that the excretion can be determined by any one of these methods:

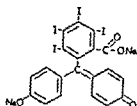
1. Its disappearance from the blood stream: S. M. Rosenthal (*J. Pharmacol. & Exper. Therap.* 19: 385 [June] 1922); H. H. Rosenfield and E. F. Schneiders (*J. A. M. A.*, March 17, 1923, p. 743).

2. The excretion of the drug in the duodenum by means of a duodenal tube: Aaron, Beck and Schneider (*J. A. M. A.*, Nov. 19, 1921, p. 1631).

3. The excretion of the drug in the stool: Rowntree, Hurwitz and Bloch (*J. Biol. Chem.* 44: 227, 1921); Whipple, *P.* 24: 343, 1911; *A. Phys. &*

Dosage.—Five milligrams in the form of disodium phenoltetrachlorophthalein per Kg. of body weight, intravenously. The solution must not be exposed unduly long, as the salt is sensitive to the action of the carbon dioxide of the atmosphere.

PHENTETIOTHALEIN SODIUM.—Iso-Iodeikon
alein Sodium.—NaO.O:
halein sodium contains
The structural formula



For tests and standards, see Section B

time for cholecystography and liver function test Following the intravenous injection the solution appears in the normal gall-

caution

Dosage—Intravenously for visualization of the gallbladder and simultaneous test of liver function, 40 mg per kilogram of body weight, the dose need not exceed 25 Gm., regardless of weight The dye is dissolved in about an ounce of freshly distilled water, filtered through fine filter paper, and sterilized for fifteen minutes in a boiling water bath The solution should be freshly made not more than twenty-four hours before it is used It is injected intravenously by gravity with about 150 cc of Ringer's solution in not less than fifteen minutes, either in the morning between 8 and 9 or in the evening between 5 and 9 If given in the evening the evening meal should be omitted and no food given until the first roentgenogram is taken in the morning At this time a fat meal is given and the roentgenogram taken one hour after the meal and, if desired, another three hours after the meal to determine the rapidity and characteristics of emptying More satisfactory results are probably

added to 120 to 240 cc of grape juice, to be taken during and after the evening meal, which should be of the usual amount but free of fat (the aqueous solution of the drug should not be more than 48 hours old) Meticulous roentgen ray technic is necessary, and if the interpretation of the cholecystogram is in question a check determination should be made either by the

oral or, if preferred, by the intravenous method. The liver function test cannot be made by this method because the dye is not absorbed rapidly enough into the blood.

To make the determination of liver function blood collected he intra- drop of to a set of standard solutions as suggested by Dazenthal (Am J Pharmacol 1929).

Journal (April 1929).

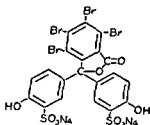
MALLINCKRODT CHEMICAL WORKS

Iso-Iodeikon (*Granules*); Bulk.

Iso-Iodeikon (*Granules*); 2.5 Gm. ampuls.

U. S. trademark 213,690

S. I. O. B. R. O. M. O. P. H. T. H. A. L. E. I. N. SODIUM-U. S. P.—
 B. & D.).—Disodium phenol-
 th disodium salt formed by
 pl acid (or anhydride) and
 It contains from 37 to 38
 per cent of bromine. The structural formula may be represented
 as follows:



For standards, see the U. S. Pharmacopeia under Sulfobromophthalein Sodium and Sulfobromophthalein Sodium Injection.

Actions and Uses.—Sulfobromophthalein sodium is used intravenously in 5 per cent solution as a test of liver function. Normally, it is rapidly removed from the blood stream by the liver (excreted in the bile); the time required for its removal is dependent on the size of the dose and the functional capacity of the liver. Test doses of 2 mg. or 5 mg. of the drug per 100 lb. of body weight are normally completely removed from the blood stream within 15 to 30 minutes. In

parison with a set of suitably prepared standards, depending on the size of the test dose used.

Retention of dye in the blood is a useful test in the diagnosis of liver disease. The dye is injected into the vein and its retention in the blood is measured at the end of a given interval, but may be irritant to the tissues. Reactions to the compound itself are rare, but have occurred, especially with the use of the 5 mg dose in obese patients.

Injection for estimation of dye retention are perhaps better fixed according to the normal periods for total clearance of these doses 20 and 45 minutes respectively. The 5 mg dose is considered to give more sensitive results, so that the normal amount of dye retained in the blood one hour after its administration is less than 6 per cent. Impairment of liver function will show a retention of dye from 6 to 40 per cent or more.

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HYNSON, WESTCOTT & DUNNING INC.

Bromsulphalein Sodium (Powder) Bulk

Solution Bromsulphalein Sodium 5% 3 cc ampuls

U S trademark 373 899 (Dec. 26 1939)

Toxins for Immunity Tests

(See Chapter on Serums and Vaccines Diagnostic Agents)

Allergenic Extracts Diagnostic

(See Chapter on Allergenic Preparations)

MERCURY COMPOUNDS

Acid-producing diuretics such as ammonium chloride administered orally prior to injection of the mercurials have been shown to increase the diuretic effect of the latter.

The reported fatalities following injection of mercury diuretics have all occurred after intravenous administration. Since these diuretics are effective and relatively safe when administered by intramuscular injection, this appears to be the route of choice.

Mercury diuretics are proposed for use in cardiac edema; nephrotic edema; ascites of liver disease; and in carefully selected cases of subacute and chronic forms of nephritis. The diuresis from the mercurials not only eliminates water, but also causes the elimination of sodium which diminishes the ability of the body to retain fluid. They are contraindicated in acute nephritis and in chronic kidney disease in which well defined tubular and glomerular changes are present.

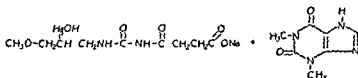
Since mercury is known to give rise in sensitive patients to side effects such as stomatitis, gastric disturbances, vertigo, febrile reactions, and cutaneous eruptions, it is suggested that initial tests and careful regulation of dosage be followed when mercury diuretics are used. It should be recognized, however, that some patients may be sensitive to one mercurial, yet tolerate another satisfactorily. Demonstrated sensitivity to one mercurial is not necessarily proof that all mercury diuretics are contraindicated.

During prolonged administration of mercurial diuretics the urine should be examined periodically for albumin, casts and blood cells.

Diabetic infants at intervals regulated to maintain freedom
weight have been
response, repeated

MERALLURIDE SODIUM SOLUTION

U. S. PAT. 2,205,941



For tests and standards see Section B

Actions and Uses—Meralluride sodium solution is a mercurial diuretic proposed for use in the edema of cardiorenal disease and of nephrosis, ascites of liver disease and other conditions in which a mercurial diuretic may be indicated.

It is well tolerated systemically and seldom causes pain at the site of injection when given intramuscularly. It is rapidly absorbed following intramuscular injection. It also is administered by intravenous injection.

The drug is contraindicated in acute nephritis and chronic kidney disease in which well defined tubular and glomerular

and blood cells

Dosage—Depending on the condition of the patient and route and the frequency of administration, the usual dose of meralluride sodium solution is from 1 cc. to 2 cc. In view of occasional cases of idiosyncrasy to mercurials the initial dose could be 0.5 cc. or less. Subsequent injections may be given twice weekly, as indicated by the condition of the patient. One investigator has recommended smaller doses repeated at shorter intervals and emphasizes the importance of observing daily water balance instead of weekly observations.

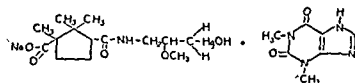
LANESIDE LABORATORIES INC.

Solution Mercurhydrin Sodium 1 cc. and 2 cc. ampuls

U. S. patent 2,205,941

MERCUROPHYLLINE INJECTION—U. S. P.—Mercuranthin (CAMPELL PRODUCTS)—A sterile solution in water for injection of the sodium salt of β methoxy- γ hydroxymercuri

propylamide of trimethyl cyclopentane dicarboxylic acid ($C_{14}H_{24}NO_5HgNa$) (the mercuri compound) and of theophylline in approximately molecular proportions. It contains an amount of mercury (Hg) equivalent to not less than 37 per cent and not more than 42 per cent of the labeled amount of the mercury compound, and theophylline equivalent to not less than 93 per cent and not more than 107 per cent of the labeled amount of theophylline ($C_7H_8N_4O_2 \cdot H_2O$).—U. S. P.—The structural formula of mercuriophylline injection may be represented as follows:



For description and standards see the U. S. Pharmacopeia under Mercuriophylline Injection.

Actions and Uses.—Mercuriophylline injection is a potent

restrict the intake of sodium chloride too drastically, as copious diuresis may give rise to the symptoms associated with hypochloremia. This effect can probably be overcome by using ammonium chloride while allowing the benefits of sodium depletion. Mercuriophylline is also available in tablet form.

Dosage.—Intramuscularly an amount equivalent to 0.1 Gm. of the mercury compound and 40 mg. of theophylline mono-

cent
centi-
-rcury

ssive

edema, approximately 275 mg administered at one time will usually produce a response comparable to that obtained with repeated injections. In severe cases reaccumulation of the dropsical fluid may be partly or entirely controlled with 60 mg to 110 mg daily, while in milder cases with occult edema 60 mg to 110 mg three successive days is sufficient. The effect of the drug on the symptoms of cardiac failure may be enhanced by the administration of a low-salt diet. The mouth on the day pre-

CAMPBELL PRODUCTS INC.

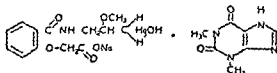
Solution Mercuzanthin 135 mg per cc 1 cc and 2 cc ampuls

Enteric Coated Tablets Mercuzanthin Each enteric coated tablet contains a concentrate representing 0.74 cc. of mercurphylline injection U S P equivalent to 30 mg of mercury and 27 mg of anhydrous theophylline

U S patent 2 117 901 U S trademark 419 384

S P.—Salv-
ture contain
in {ortho(hy
acetate — for
heophylline.—

U S P The structural formula of mersalyl and theophylline may be represented as follows



For description and standards see the U S Pharmacopeia under Mersalyl and Theophylline Injection.

Actions and Uses—Mersalyl and theophylline has been demonstrated to produce less local reaction on intramuscular or intravenous injection than mersalyl alone and to be somewhat

gastric disturbance more or less diarrhea vertigo headache febrile reaction and cutaneous eruptions When the use of mer

salyl and theophylline is continued over a prolonged period of time the urine should be examined from time to time for albumin, casts and blood cells. Sudden fatalities have been reported following the use of these drugs while these times these d available evi mechanism o exercised in p rhythmia, for example, patients with frequent ventricular beats, heavily digitalized patients, or those with recent myocardial infarction.

Dosage.—For Adults: Intramuscularly or intravenously mersalyl, 0.2 Gm. and theophylline, 0.1 Gm. For susceptibility, test the patient with one-half of the recommended dose. If well tolerated, the recommended dose may be given on the following day. In some cases this may have to be doubled for the full effect. Usually injections are not given more frequently than every three or four days. After relief of the dropsy, recurrences can often be prevented by occasional injections. One dose of about 0.3 Gm. may be given in the morning after breakfast and repeated in four to five days if required. As an adjunct to intravenous medication, about 0.1 Gm. may be given daily for one or two weeks but in such instances rest periods of one or two weeks should intervene between courses of treatment. For Children: The above recommendations should be reduced by one-half.

WINTHROP-STEARNs, INC.

Solution Salyrgan-Theophylline: 1 cc. and 2 cc. ampuls. Each cc represents Mersalyl and Theophylline Injection U. S. P.

Enteric Tablets Salyrgan-Theophylline: Each tablet contains 80 mg mersalyl and 40 mg theophylline and is coated with shellac.

U. S. patent 2,213,457 (Sept. 3, 1940; expires 1957). U. S. trademark 188,515

MERSALYL AND THEOPHYLLINE INJECTION.

U. S. P.—“A sterile solution in water for injection of approximately 10 parts by weight of mersalyl ($C_{13}H_{18}HgNO_8Na$) to each 5 parts by weight of theophylline ($C_7H_8N_4O_2 \cdot H_2O$). It contains mercury (Hg) equivalent to not less than 37 per cent and not more than 42 per cent of the labeled amount of ($C_{13}H_{18}HgNO_8Na$) and not less than 93 per cent and not more than 107 per cent of the labeled amount of ($C_7H_8N_4O_2 \cdot H_2O$).”—U. S. P.

For description and standards see Mersalyl and Theophylline Injection in the U. S. Pharmacopeia.

Actions and Uses.—See monograph on Mersalyl and Theophylline.

Dosage.—See monograph on Mersalyl and Theophylline.

UREA

UREA-U. S. P.—Carbamide Its structural formula may be represented as follows



For description and standards see the U. S. Pharmacopoeia under Urea.

Actions and Uses—Urea is an active diuretic; it is rapidly eliminated and is not poisonous. It is useless in the treatment of tuberculosis and has no important solvent action on urinary calculi. It may be employed when diuresis is indicated though it appears irrational in any renal disease characterized by retention of nitrogen. Urea should not be used as a diuretic when there is impaired elimination. Concentrated solutions of urea dissolve protein readily, but have little action on healthy tissue, hence urea has been used for the removal of necrotic tissue in infected wounds, and for the removal of foul odors. Certain observers believe that even weak solutions stimulate granulation and hasten the healing of wounds.

Dosage—From 0.5 to 4 Gm. Urea is given in solution, or it may be enclosed in cachets.

MALLINCRODT CHEMICAL WORKS

Urea (Crystals) Bulk

XANTHINE DERIVATIVES

Caffeine, theobromine and theophylline are methyl xanthines, derived from xanthine by the introduction of two or three methyl radicals into a corresponding number of NH_2 groups. As these may occupy various positions in the xanthine nucleus a considerable number of methyl xanthines exist, naturally or by synthesis, differing quantitatively in pharmacologic activity. Those named, however, are the only ones of therapeutic importance, namely, caffeine (1, 3, 7 trimethylxanthine), theobromine (3, 7 dimethylxanthine), and theophylline (1, 3 dimethylxanthine).



Caffeine is usually obtained from tea or coffee, theobromine is obtained from cacao, or is made synthetically. Theophylline occurs in nature but in amounts too small to be commercially available. It is prepared synthetically. Theocin is a proprietary name for synthetic theophylline.

Actions and Uses.—Theobromine and theophylline surpass caffeine in their diuretic, and perhaps in cardiac and muscular actions. They are, therefore, generally preferred in cardiac edemas, etc., since they are equally, or more, effective, more prompt and largely avoid the unpleasant side effects (insomnia, nervousness, gastric disturbance) which often interfere with the use of caffeine in adequate doses. This freedom from side

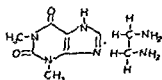
their usefulness. They are therefore used almost exclusively in the form of the readily soluble double salts, which they form with a considerable amount of compounds: theobromine and sodium salicylate, theophylline acetate-U. S. P., theophylline and aminophylline-U. S. P.

The clinical use of theobromine has been largely abandoned for most practical purposes in favor of the slightly more active

to suppose that the particular salt used to procure the solubility has any material influence on the action. The dosage of these added compounds is also generally too small to produce therapeutic effects. It may, therefore, be assumed that the various preparations which have been introduced are strictly equivalent.

Theophylline and Theophylline Compounds

AMINOPHYLLINE-U. S. P.—Theophylline Ethylenediamine.—“Contains not less than 75 per cent and not more than 80 per cent (N₄O₂), and 10 per cent of structural



For description and standards see the U. S. Pharmacopeia under Aminophylline, Aminophylline Injection and Aminophylline Tablets.

Actions and Uses—Aminophylline shares the actions and uses of other theophylline compounds over which it has the advantage of greater solubility. It is useful as a diuretic and myocardial stimulant for the relief of pulmonary edema or paroxysmal dyspnea of congestive heart failure. Its cardiac effects are considered more pronounced than those produced by other xanthine derivatives and in addition to the increase in cardiac output and work of the heart induced by myocardial stimulation the drug produces a diminution of venous pressure in congestive heart failure. There is no basis for claims that the xanthines effectively control arterial hypertension. Increased coronary blood flow which follows rather than precedes myocardial stimulation cannot be considered an adequate basis to support claims for use of the drug in coronary disease or angina pectoris. While prompt relief of pain has occasionally been observed to follow the administration of this drug in cardiac infarction this apparently beneficial effect is secured only rarely and there is always danger that the stimulating action of the drug will harm a heart handicapped by a reduced blood supply. Its prophylactic use to prevent either paroxysmal dyspnea of cardiac origin or the pain of coronary disease is considered undependable and therefore unestablished. There is lack of sufficient evidence to substantiate claims for the use of the drug in peripheral vascular disease.

Aminophylline is also useful in the control of Cheyne Stokes respiration and for the treatment of paroxysms of bronchial asthma or status asthmaticus. It is primarily useful in asthma that is refractory to epinephrine and is considered safer than epinephrine for paroxysmal dyspnea in which the bronchial or cardiac nature of the attack has not been determined.

Dosage—Aminophylline is considered effective by oral administration (tablets) and by rectal administration (suppositories or retention enema) in doses of from 0.1 Gm to 0.5 Gm only as a diuretic. Although used prophylactically by these routes for other purposes such use is considered neither reliable nor established. Like other xanthines aminophylline produces gastric irritation which limits to some degree the dosage that may be administered orally. This may account entirely for the marked difference in its effectiveness when given by injection.

Aminophylline is effective by intravenous or intramuscular injection as a diuretic, cardiac stimulant for lowering venous pressure for paroxysmal cardiac dyspnea, Cheyne Stokes respiration and acute paroxysms of bronchial asthma or status asthmaticus in doses of from 0.25 Gm to 0.5 Gm. The intravenous route is preferred because intramuscular injection may be painful. Subcutaneous injection, even more painful is not recommended. Intravenous injection should be performed slowly to avoid untoward effects.

Aminophylline is also effective by inhalation as an aerosol in the control of dyspnea of cardiac or asthmatic origin. Its beneficial effects by inhalation for other purposes have not as yet been adequately studied.

AMERICAN PHARMACEUTICAL CO., INC.

Suppositories Aminophylline: 0.5 Gm. in a water miscible base which dissolves in body fluids under conditions of use.

Tablets Aminophylline: 0.1 Gm. and 0.195 Gm.

Enteric Coated Tablets Aminophylline: 0.2 Gm.

BARLOW-MANEY LABORATORIES, INC.

Tablets Aminophylline: 0.1 Gm. and 0.2 Gm.

Enteric Coated Tablets Aminophylline: 0.1 Gm. and 0.2 Gm.

BARRY BIOLOGICAL LABORATORY, DIVISION OF BARRY LABORATORIES, INC.

Solution Aminophylline: 0.50 Gm., 2 cc. and 20 cc. ampuls and 0.25 Gm., 10 cc. ampuls.

ERNST BISCHOFF COMPANY, INC.

Tablets Aminophylline: 0.1 Gm.

GEORGE A. BREON & CO

Solution Aminophylline: 0.25 Gm., 10 cc. ampuls and 0.5 Gm., 20 cc. ampuls.

Solution Aminophylline with Benzyl Alcohol 2%: 0.48 Gm 2 cc. ampuls.

Tablets Aminophylline: 0.1 Gm. and 0.2 Gm.

BREWER & CO., INC.

Solution Aminophylline: 24 mg, 10 cc. ampuls.

Solution Aminophylline with Benzyl Alcohol 2%: 48 mg., 2 cc. ampuls.

BRISTOL LABORATORIES, INC.

Solution Aminophylline: 0.48 Gm., 2 cc. ampuls and 0.24 Gm., 10 cc. ampuls.

COLE CHEMICAL COMPANY

Tablets Aminophylline: 0.1 Gm

Solution Aminophylline: 0.5 Gm., 2 cc. ampuls with benzyl alcohol 1.5 per cent.

H. E. DUBIN LABORATORIES, INC.

Aminophylline (*Powder*): 15 Gm, 113 Gm., and 454 Gm bottles.

Solution Aminophylline: 0.24 Gm, 10 cc. ampuls, 0.48 Gm, 2 cc. and 0.48 Gm, 20 cc. ampuls.

Tablets Aminophylline: 0.1 Gm. and 0.2 Gm.

Enteric Coated Tablets Aminophylline 0.2 Gm

Rectal Suppositories Aminophylline 0.36 Gm and 0.5 Gm

ENDO PRODUCTS INC.

Tablets Aminophylline 0.1 Gm

Solution Aminophylline with Benzyl Alcohol 2%
0.48 Gm 2 cc ampuls and 0.24 Gm 10 cc. ampuls

ESTRO CHEMICAL CO., INC

Solution Aminophylline 0.25 Gm 10 cc ampuls 0.5 Gm
2 cc and 20 cc. ampuls

GANE AND INGRAM INC.

Aminophylline (*Powder*) Bulk

GOLD LEAF PHARMACAL CO

Solution Aminophylline 0.5 Gm. 2 cc and 20 cc. ampuls
and 0.25 Gm 10 cc ampuls

THE HARROWER LABORATORY INC

Tablets Aminophylline 0.1 Gm

INGRAM LABORATORIES INC.

Solution Ingraloids Aminophylline 0.243 Gm 2 cc and
10 cc ampuls and 0.486 Gm 2 cc 10 cc and 20 cc ampuls

KREMERS URBAN CO

Solution Aminophylline 0.24 Gm 10 cc ampuls and 0.48
Gm 20 cc ampuls

Solution Aminophylline with Benzyl Alcohol 2% 0.48
Gm 2 cc ampuls

Tablets Aminophylline 0.1 Gm. and 0.2 Gm

LAKESIDE LABORATORIES INC

Solution Aminophylline 0.24 Gm 10 cc ampuls and 0.48
Gm 20 cc ampuls

LEDERLE LABORATORIES DIVISION AMERICAN CYANAMID CO

Solution Aminophylline 0.25 Gm. 10 cc ampuls and 0.50
Gm 2 cc ampuls

Tablets Aminophylline 0.1 Gm and 0.2 Gm.

LINCOLN LABORATORIES INC.

Solution Aminophylline 0.48 Gm 2 cc and 20 cc. ampuls
and 0.24 Gm 10 cc ampuls

S. E. MASSENGILL COMPANY

Tablets Aminophylline 0.1 Gm and 0.19 Gm.

MERCK & Co., INC.

Theophylline Ethylenediamine (*Powder*): 30 Gm., 12½ Gm. and 498 Gm. bottles.

THE WM. S. MERRELL CO.

Solution Aminophylline: 0.45 Gm., 2 cc. ampuls and 0.25 Gm., 10 cc. ampuls.

Tablets Aminophylline: 0.1 Gm.

E. S. MILLER LABORATORIES, INC.

Solution Theophylline Ethylenediamine 2.4%: 10 cc. and 20 cc. ampuls.

Solution Aminophylline 24% W/V in Ethylenediamine
Solution 1% V/V with Benzyl Alcohol 2% V/V: 2 cc. ampuls.

Tablets Theophylline Ethylenediamine: 90 mg. and 180 mg.

PHARMEDIC CORPORATION

Aminophylline (*Powder*): Bulk.

Solution Aminophylline: 0.24 Gm., 10 cc. ampuls and 0.48 Gm., 2 cc. ampuls.

Suppositories Aminophylline: 0.36 Gm.

Tablets Aminophylline: 0.1 Gm.

PREMO PHARMACEUTICAL LABORATORIES, INC.

Aminophylline (*Powder*): 28.35 Gm. and 113.39 Gm. bottles.

Enterals Aminophylline: 0.1 Gm. and 0.2 Gm. enteric coated.

Tablets Aminophylline: 0.1 Gm. and 0.2 Gm.

Solution Aminophylline: 0.25 Gm., 10 cc. ampuls and 0.5 Gm., 2 cc. ampuls.

Suppositories Aminophylline: 0.5 Gm. in a water soluble Carbowax base.

RAYMER PHARMACAL COMPANY

Solution Aminophylline: 0.26 Gm., 10 cc. ampuls and 0.48 Gm., 20 cc. ampuls.

Solution Aminophylline with Benzyl Alcohol 2%: 0.48 Gm., 2 cc. ampuls.

Suppositories Aminophylline: 0.5 Gm.

Tablets Aminophylline: 97 mg. and 0.194 Gm.

Enteric Coated Tablets Aminophylline 97 mg and 0.194 Gm. Each tablet is enteric coated with a mixture of sandarac and phenyl salicylate

WILLIAM H. RORER, INC.

Solution Aminophylline 0.24 Gm. 10 cc. ampuls

G. D. SEARLE & CO.

Aminophyllin (Powder) Bulk

Solution Aminophyllin 0.25 Gm., 10 cc. ampuls and 0.5 Gm., 20 cc. ampuls for intravenous injection.

Solution Aminophyllin with Benzyl Alcohol 2% 0.5 Gm. 2 cc. ampuls with benzyl alcohol 2 per cent for intramuscular injection.

Tablets Aminophyllin 0.1 Gm and 0.2 Gm

Enteric Coated Tablets Aminophylline 0.1 Gm. and 0.2 Gm.

Suppositories Aminophyllin 0.50 Gm. Each suppository contains aminophyllin, 0.50 Gm. incorporated into a specially compounded wax base which will not liquefy in storage at temperatures up to 130 F but which disintegrates readily under conditions of use.

CARROLL DUNHAM SMITH PHARMACEUTICAL COMPANY

Solution Aminophylline 0.25 Gm. 10 cc. ampuls and 0.5 Gm., 20 cc. ampuls

Solution Aminophylline with Benzyl Alcohol 2% 0.5 Gm. 2 cc. ampuls

Tablet Aminophylline 0.1 Gm

Enteric Coated Tablets Aminophylline 0.2 Gm. Each tablet is enteric coated with shellac.

SMITH DORSEY COMPANY

Solution Aminophylline 0.5 Gm., 2 cc. and 20 cc. ampuls and 0.25 Gm. 10 cc. ampuls

Suppositories Aminophylline 0.5 Gm. in a water soluble Carbowax base.

Tablets Aminophylline 0.1 Gm. and 0.2 Gm.

THE VALE CHEMICAL CO., INC.

Enteric Coated Tablets Aminophylline 0.1 Gm. and 0.2 Gm. Each tablet is enteric coated with a coating composed of white glue, castor oil and calcium carbonate

Tablets Aminophylline 0.1 Gm.

WARREN-TEED PRODUCTS COMPANY

Tablets Aminophylline: 0.1 Gm.

WYETH INCORPORATED

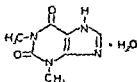
Suppositories Aminophylline: 0.5 Gm.

ZEMMER CO., INC.

Tablets Aminophylline: 0.1 Gm. and 0.2 Gm.

Enteric Coated Tablets Aminophylline: 0.1 Gm. and 0.2 Gm. Each tablet is enteric coated with a mixture of keratin and shellac.

THEOPHYLLINE-U. S. P.—Theocin (WINTHROP-STEARN'S).—The structural formula may be represented as follows:



For description and standards see the U. S. Pharmacopeia under Theophylline and Theophylline Tablets.

diuretic response is not as lasting; for this reason, it is advisable to replace it after two or three days by theobromine. Theophylline may produce gastric and, perhaps, renal irritation.

Dosage.—0.25 Gm. three times daily.

MERCK & CO., INC.

Theophylline (*Crystals*): 30 Gm., 124 Gm. and 498 Gm. bottles.

E. S. MILLER LABORATORIES, INC.

Tablets Theophylline: 0.1 Gm.

WINTHROP-STEARN'S, INC.

Theocin (*Powder*): Bulk. Prepared synthetically.

Preparation—

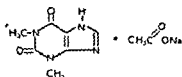
Theocin is obtained by heating the monoformyl derivative of 1,3-

Tablets Theocin: 0.1 Gm.

U. S. patent 216,994 (Dec. 30, 1902; expired). U. S. trademark 39,115.

THEOPHYLLINE AND SODIUM ACETATE.

U. S. P.—Theocin Soluble (WINTHROP-STEARN'S)—A hydrated mixture of theophylline sodium ($C_7H_7N_4O_2Na$) and sodium acetate ($NaC_2H_3O_2$) in approximately molecular proportion. It yields not less than 55 per cent and not more than 65 per cent of anhydrous theophylline ($C_7H_8N_4O_2$).—**U. S. P.** The structural formula may be represented as follows:



For description and standards see the U. S. Pharmacopeia under Theophylline and Sodium Acetate and Theophylline and Sodium Acetate Tablets.

Actions and Uses—It has the actions and uses of theophylline, with the advantage of being much more soluble in water.

Dosage—From 0.2 to 0.35 Gm., best given after meals.

WINTHROP-STEARN'S, INC.

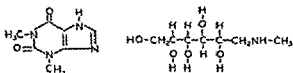
Theocin Soluble (Powder) Bulk

Tablets Theocin Soluble 0.16 Gm.

U. S. patent 716,994 (Dec. 30, 1902 expired) U. S. trademark 59,135

THEOPHYLLINE-METHYLGLUCAMINE.—**Glucophylline (Abbott)**—An equimolecular mixture of theophylline U. S. P. ($C_7H_8N_4O_2 \cdot H_2O$) and methylglucamine ($C_7H_{17}NO_5$). Dosage forms of theophylline methylglucamine contain not less than 95 per cent nor more than 105 per cent of the labeled quantities of theophylline and methylglucamine.

The structural formula may be represented as follows:



For tests and standards see Section B.

Actions and Uses—Theophylline-methylglucamine is identical in action and therapeutic purpose to aminophylline (theophylline ethylenediamine) U. S. P. over which it has no advantage. It is therefore similarly useful orally and by injection to produce the effects of theophylline when a more soluble salt than theophylline and sodium acetate is needed. It is employed orally as a diuretic and myocardial stimulant for pulmonary edema and paroxysmal dyspnea in congestive heart failure, and for the relief of Cheyne-

Actions and Uses—Theophylline-sodium glycinate has the typical action of other solubilized forms of theophylline such as theophylline sodium acetate and theophylline ethylenediamine (aminophylline) with the advantage that it is somewhat more stable in air and less irritating to the gastric mucosa. It is thus tolerated orally in larger doses than are possible with other theophylline preparations and it can be administered by mouth in liquid form as well as non enteric coated tablet form. It is incompatible for compounding with acidic drugs. Theophylline-sodium glycinate is only slightly less soluble than aminophylline commonly employed for the injection of theophylline but it can be administered alone or alternated with penicillin as an aerosol for inhalation in the treatment of severe bronchial asthma. Until more evidence becomes available claims for the uses of theophylline sodium glycinate are restricted to those recognized for aminophylline its value in cardiac conditions other than paroxysmal cardiac dyspnea is considered to be unestablished.

Dosage—Theophylline sodium glycinate consists of approximately 50 per cent of anhydrous theophylline whereas aminophylline consists of approximately 80 per cent. The dose of theophylline-sodium glycinate would thus be expected to be about one third more than aminophylline.

Orally either as powder tablets elixir or syrup. Adults 0.3 Gm. to 1.0 Gm. children over 12 years, 0.15 Gm. to 0.4 Gm., children 6 to 12 years 0.1 Gm. to 0.2 Gm. every four to six hours. The powder or tablets are preferably administered with water after meals. Suppositories are recommended only for adults until rectal doses for children are established. The adult rectal dose is 0.78 Gm. every 4 to 6 hours. Oral doses for children under 6 years are also unestablished.

Theophylline sodium glycinate may be administered as an aerosol by nebulization with oxygen of a 5 to 10 per cent solution for inhalation, preferably under a canopy. Nebulization of 2 cc. of such a solution every four hours may be effective in refractory cases of bronchial asthma. Very severe dyspnea may require continuous therapy or alternate inhalation of nebulized anti infective agents such as penicillin.

BRAYTEX PHARMACEUTICAL COMPANY

Theoglycinate (Powder) Bulk, 113 Gm. bottles

Suppositories Theoglycinate 0.78 Gm.

Syrup Theoglycinate 0.13 Gm. per 4 cc., 240 cc. bottles.

Tablets Theoglycinate 0.325 Gm.

U S patent 2,433,765 U S trademark 501,300.

THE CENTRAL PHARMACAL COMPANY

Synophylate (Powder) 113 Gm and 454 Gm. bottles.

Suppositories Synophylate 0.78 Gm.

Syrup Synophylate: 0.33 Gm. per cc., 480 cc. and 384 liter bottles.

Tablets Synophylate: 0.33 Gm.

Licensed under U. S. patent 2,433,765, U. S. trademark pending

FIRST TEXAS CHEMICAL MFG. CO.

Glynazan (Powder): 113 Gm. and 454 Gm. bottles

Elixir Glynazan: 0.26 Gm per 4 cc., 480 cc. and 384 liter bottles.

Syrup Glynazan: 0.13 Gm. per 4 cc., 480 cc. and 384 liter bottles.

Tablets Glynazan: 0.324 Gm.

Licensed under U. S. patent 2,433,765; U. S. trademark pending.

THE E. L. PATCH COMPANY

Glytheonate (Powder): 113 Gm and 454 Gm. bottles.

Suppositories Glytheonate: 0.78 Gm.

Tablets Glytheonate: 0.324 Gm.

Licensed under U. S. patent 2,433,765, U. S. trademark pending

Gastro-intestinal Drugs

The class of drugs which act on the gastro-intestinal tract includes only a few. Certain other drugs that have marked effects on the secretions and movements of the gastro-intestinal tract will be found in the chapter on Autonomic Drugs.

ANTACIDS

ALUMINUM HYDROXIDE GEL—N. N. R.—Creamalin (WINTHROP-STEARN) —An aqueous suspension containing not less than 3 per cent nor more than 4.4 per cent of aluminum oxide, chiefly in the form of aluminum hydroxide. Flavoring, sweetening and preservatives may be added.

See also standards of the U. S. Pharmacopeia under Aluminum Hydroxide Gel.

For tests and standards, see Section D.

Actions and Uses—Aluminum hydroxide gel has been shown to be an effective gastric antacid neutralizing hydrochloric acid of the stomach by chemical reaction. It does not increase the pH of the gastric juice beyond the point which interferes with pepsin digestion, does not stimulate a compensatory increase in gastric acidity.

are the principal indications. Its use is of clinical significance because it reacts as an acid only.

above 9 such a pH is not normal in the gastric tract. Its so-called bismuth effect is not real.

It is presumed that aluminum hydroxide is formed by the reaction of aluminum oxide with water.

acid in the stomach, it is not a true antacid.

other aluminum compounds are also used as antacids.

5 mild astringent and has some importance in the treatment of peptic ulcers. Some evidence also suggests that its effectiveness may be further explained by the tendency to increase mucin secretion and to precipitate pepsin.

As a result, it is not an antacid in the strict sense of the word.

4 not absorbed to any extent.

astringent.

GEORGE A. BREON & COMPANY, INC.

Tablets Dehydrocholic Acid: 0.25 Gm.

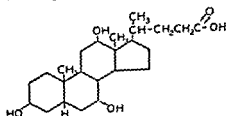
THE HARROWER LABORATORY, INC.

Tablets Dehydrocholic Acid: 0.243 Gm.

E. S. MILLER LABORATORIES, INC.

Tablets Dehydrocholic Acid: 0.243 Gm.

OX BILE EXTRACT—U. S. P.—Bilein (Abbott).—Glycotauro (H. W. & D.).—Bile Salts.—"Contains an amount of the sodium salts of ox bile acids equivalent to not less than 45 per cent of cholic acid ($C_{24}H_{40}O_5$)."
U. S. P. The structural formula of cholic acid may be represented as follows:



For description and standards see the *U. S. Pharmacopeia* under Ox Bile Extract

The bile of man and of several animals contains the sodium salts of several conjugated oxycholanolic acids in varying proportions. In ox and human biles glycocholic acid and taurocholic acid are prominent constituents. Fresh ox bile is said to contain about 3 per cent each of sodium glycocholate and sodium taurocholate.

Actions and Uses.—The bile salts constitute the main active principles of bile, and therefore share the actions and uses of the latter, perhaps with the advantage of more constant composition. When injected into the circulation, they cause severe nervous and cardiac depression, not observed when they are given by the mouth. They are generally credited with a slight antiseptic and laxative action, with enhancing the efficiency of the resinous hydragogue cathartics, and a prominent role in the digestion and absorption of fat. They stimulate the secretory activity of the liver, increasing both the fluids and solids of the bile.

They have been used with doubtful rationale in obstructive jaundice; their use is more reasonable in nutritional disturbances accompanying biliary fistula. There is evidence to indicate that bile salts are useful to promote the intestinal absorption of food fats and fat soluble vitamins when failure to absorb these substances is due to lack of bile in the intestine.

Dosage.—From 0.2 Gm. to 0.4 Gm. with water, preferably after meals.

Preparation.—Ox bile extract is made either by dissolving ox bile in al-

ABBOTT LABORATORIES

Bilein: Dried and purified ox bile. A powdered preparation of ox bile containing not less than 70 per cent of total bile acids essentially in the form of sodium glycocholate and sodium taurocholate, in the proportion existing in ox bile.

Capsules Bilein: 0.3 Gm Each capsule contains sodium chloride 30 mg as an excipient

Tablets Bilein: 0.2 Gm Each tablet contains 12 mg each powdered magnesium oxide, U S P and talc as excipients

Enterab Tablets Bilein 0.2 Gm Each tablet contains 12 mg each of powdered magnesium oxide, U S P and talc as excipients and is enterically coated.

U S trademark 44 140

HYNSON, WESTCOTT & DUNNING INC.

Capsules Glycotauro 85 mg Concentrated ox bile, freed from bile pigments, containing more than 50 per cent of the natural mixture of sodium glycocholate and sodium taurocholate Each gram represents approximately 15 cc of fresh ox bile

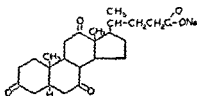
Enteric Coated Tablets Glycotauro 78 mg Each tablet is enteric coated with salol

WINTHROP STEARNS INC

Bile Salts Bulk. A preparation obtained from fresh ox bile, consisting essentially of sodium glycocholate and sodium taurocholate, in the proportion existing in ox bile

Capsules Bile Salts 0.2 Gm

SODIUM DEHYDROCHOLATE—Decholin Sodium (AMES) —The structural formula may be represented as follows



For tests and standards, see Section B

Actions and Uses—The actions and uses of sodium dehydrocholate are the same as those of dehydrocholic acid

After intravenous injection decholin sodium is a mild diuretic. It has been shown to produce diuresis in edematous patients when this edema is of cardiac origin, but it is less effective than the mercurials for this purpose. However, as is the case with certain other mild diuretics, when given with the mercurials it potentiates their diuretic effect.

Sodium dehydrocholate is also useful in the treatment of the arm to tongue circulation conditions affecting the velocity of circulation.

Sodium dehydrocholate is also useful in the treatment of bronchial asthma.

Dosage.—Sodium dehydrocholate is given intravenously. One injection is given from 5 to 10 cc. of the 20 per cent solution; the second and third, of 10 cc.

The time is recorded from the beginning of injection to the perception of a bitter taste (average normal range 9 to 16 seconds).

AMES COMPANY, INC.

Solution Dêcholin Sodium, 20%: 3 cc., 5 cc., and 10 cc. ampuls.

U. S. trademark 315,083.

GEORGE A. BREON & COMPANY, INC.

Solution Sodium Dehydrocholate 20%: 5 cc. ampuls.

ENDO PRODUCTS, INC.

Solution Sodium Dehydrocholate 20%: 3 cc. and 10 cc. ampuls.

CARROLL DUNHAM SMITH PHARMACAL CO.

Solution Sodium Dehydrocholate 20%: 5 cc. vials.

EMOLLIENTS

GASTRIC MUCIN.—The fraction precipitated by approximately 60 per cent alcohol from the supernatant liquid after pepsin-hydrochloric acid digestion of hog stomach linings.

For tests and standards, see Section B.

Actions and Uses.—Gastric mucin is prepared for use in the treatment of peptic ulcers.

Dosage.—Average dose 2.5 Gm., which can be given at two hour intervals.

Gastric mucin is manufactured by license from the Gastric Mucin Committee of Northwestern University Medical School under U. S. patent 1,829,270 (Oct. 27, 1931; expires 1948).

THE ARMOUR LABORATORIES

Gastric Mucin (*Granules*) 2268 Gm and 4536 Gm packages

Gastric Mucin (*Powder*) 2268 Gm. and 4536 Gm. packages

WILSON LABORATORIES

Gastric Mucin (*Granules*) 2268 Gm and 4536 Gm packages

Gastric Mucin (*Powder*) 4536 Gm packages

WINTHROP STEARNS INC.

Gastric Mucin (*Granules*) 5 Gm and 2268 Gm packages

Gastric Mucin (*Powder*) 2268 Gm and 4536 Gm. packages

BISMUTH MAGMA N F—Cremo Bismuth (SHARP & DOHME)—Lac Bismo (HART)—"Bismuth Magma contains bismuth hydroxide and bismuth subcarbonate in suspension in water and yields not less than 5.2 per cent and not more than 5.8 per cent of Bi_2O_3 —N F

For description and standards see The National Formulary under Bismuth Magma

Actions and Uses—Used in digestive disturbances

Dosage.—From 4 to 15 cc. every two or three hours

E. J. HART & COMPANY, LTD

Lac Bismo

U S trademark 52,250

SHARP & DOHME, INC.

Cremo Bismuth

U S trademark 29,335

LAXATIVES

AGAR U S P.—Agar Agar—The dried hydrophilic colloidal substance extracted from *Gelidium cartilagineum* (Linne) Gallion (Fam. *Gelidiaceae*) and from related red algae (Class *Rhodophyceae*)—U S P

For description and standards see the U S Pharmacopeia under Agar

Actions and Uses—Passes through the intestinal canal almost unchanged Absorbs and retains moisture, and acts as an intestinal demulcent and lubricant Used in chronic constipation of intestinal atony renders the feces soft and bulky and thus promotes peristalsis

Dosage—4 Gm.

MERCK & Co., INC.

Agar-Agar (*Flakes and Powder*): Bulk.

LIQUID PETROLATUM EMULSION.—U. S. P.—Liquid Paraffin.—White Mineral Oil.—Heavy Liquid Petrolatum.—“A mixture of liquid hydrocarbons obtained from petroleum.” U. S. P.

For description and standards see the U. S. Pharmacopeia under Liquid Petrolatum and Liquid Petrolatum, Emulsion and the National Formulary under Petrolatum, Liquid, Emulsion with Phenolphthalein.

Actions and Uses.—Liquid petrolatum and liquid petrolatum emulsion are used for the treatment of constipation to keep the stools soft. Studies indicate that small amounts of both unemulsified and emulsified mineral oil may be absorbed by the intestine, particularly the latter, so that absorption may be a function of particle size. Although lipid granulomas are occasionally encountered in human mesenteric lymph nodes that are attributed to the absorption of mineral oil, the practical significance of these accumulations is not known. Mineral oil present in the upper part of the intestinal tract may interfere with the absorption of carotene, vitamin A, D and K, so that its use should be avoided during pregnancy and it should not be administered shortly before or after meals. The indiscriminate oral administration of mineral oil to infants may be followed by bronchial aspiration and lipid pneumonia.

Dosage.—From 15 cc. to 30 cc. orally, preferably at bedtime only, to avoid close proximity to meals.

THE E. L. PATCH COMPANY

Emulsion Kondremul (Plain): 500 cc. bottles. An emulsion of mineral oil and Irish Moss (*Chondrus Crispus*).

Emulsion Kondremul with Cascara: 400 cc. bottles. An emulsion of mineral oil with non-bitter extract of cascara and Irish Moss (*Chondrus Crispus*).

Emulsion Kondremul with Phenolphthalein: 500 cc. bottles. An emulsion of mineral oil with phenolphthalein and Irish Moss (*Chondrus Crispus*).

SMITH-DORSEY COMPANY

Emulsion Liquid Petrolatum (Chocolate Flavored): A

Emulsion Liquid Petrolatum with 0.1 Gm. Phenolphthalein (Chocolate Flavored).

Emulsion Liquid Petrolatum with 0.3 Gm. Phenolphthalein (Chocolate Flavored).

SMITH OIL & REFINING COMPANY

Mineral Oil: Bulk.

E. R. SQUIBB & SONS

Mineral Oil: 180 cc., 480 cc. and 960 cc. bottles.

Emulsion Mineral Oil: Mineral oil, 50 cc.; sodium alginate, 0.49 Gm.; methyl cellulose, 0.25 Gm.; sodium benzoate, 0.10 Gm.; glycerin, water and flavoring sufficient to make 100 cc.

Emulsion Mineral Oil and Phenolphthalein: Mineral oil emulsion with 0.33 Gm. phenolphthalein per 100 cc.

WYETH, INC.

Petrogalar: Liquid petrolatum 65 per cent emulsified with 0.4 per cent sodium alginate in a menstruum containing glycerin, agar, acacia, saccharin, flavoring, benzoic acid and water to make 100 cc. Preserved with benzoic acid 0.06 per cent.

Petrogalar Alkaline: Petrogalar with *magnesia oxide* 0.45 per cent. No saccharin or preservative.

Petrogalar with Cascara: Petrogalar with nonbitter fluid extract of cascara sagrada 13.75 per cent, karaya 0.14 per cent. Preserved with sodium benzoate 0.06 per cent.

Petrogalar with Phenolphthalein: Petrogalar with phenolphthalein 0.3 per cent. Preserved with benzoic acid 0.06 per cent.

Petrogalar Unsweetened: Petrogalar with saccharin omitted. Preserved with benzoic acid 0.06 per cent.

U. S. trademark 165,616.

PETROLATUM-U. S. P.—Petroleum Jelly—"A purified, semi-solid mixture of hydrocarbons obtained from petroleum"
U. S. P.

For description and standards see the U. S. Pharmacopeia under Petrolatum.

Actions, Uses and Dosage—Petrolatum is used chiefly as an ointment base. Sterilized petrolatum is employed as a lubricant.

SARGENT'S DRUG STORE

Petrobran: Each 100 Gm. contains petrolatum, 74 Gm.; bran, 22 Gm., with powdered licorice and "oil of pineapple" (ethyl butyrate) sufficient to flavor.

and powdered amygdalus dextrose, with sodium bicarbonate 0.4

per cent, monobasic potassium phosphate 0.25 per cent, citric acid 0.33 per cent and benzyl benzoate 0.04 per cent.

For tests and standards, see Section B.

Actions and Uses.—Psyllium hydrophilic mucilloid with dextrose is intended as an adjunct in the treatment of constipation. It encourages elimination by the formation of a soft, plastic, per bowel. The effect in the presence of the pres-mucilloid with to obtain more uniform dispersion of the barium for x-ray visualization.

Dosage.—Four to 7 Gm. one to three times daily, each dose thoroughly stirred in a glass of water and followed by an additional glass of liquid. Children receive proportionate amounts according to weight and age. It is important that adequate fluids be ingested to assure a soft bulk. Psyllium hydrophilic mucilloid with dextrose should not be used carelessly so that a state of dependency is reached.

G. D. SEARLE & Co.

Metamucil: 113 Gm., 227 Gm. and 454 Gm. containers.

U. S. patent 2,095,259 (Oct. 12, 1937; expires 1954), U. S. patent 2,132,484 (Oct. 11, 1938; expires 1955), U. S. trademark 317,704 (Oct. 2, 1934).

Hematics

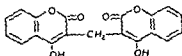
This chapter includes agents that exert an effect on the blood itself. It thus comprises principally (1) agents that influence the production of formed elements and (2) agents that affect the coagulation of the blood.

The former group includes iron compounds and certain

Vitamin Preparations

ANTICOAGULANTS

DICUMAROL. — 3,3'-methylenebis(4-hydroxycoumarin) — The structural formula of dicumarol may be represented as follows:



For tests and standards, see Section B

Actions and Uses — Dicumarol causes a lengthening of the

therapy

units of anticoagulant activity per milligram of dry material,

only as a standard of potency

For tests and standards see Section B

Actions and Uses—Heparin sodium has the property of inhibiting blood coagulation. It may aid the normal body to maintain blood in a fluid state as traces are detectable in the blood. Very little is known concerning the metabolism, excretion and fate of heparin sodium in the body. Its anticoagulant action appears to be effected by action on the thrombin which with fibrinogen forms fibrin.

The exact status of heparin sodium in surgery and medicine has not been determined but it is claimed to be of value as a substitute for citrate in blood transfusions in an attempt to prevent postoperative thrombosis and possibly thrombosis of

thrombosis in phlebitis
 It has been used alone
 t of subacute bacterial
 to be done before this
 procedure can be generally accepted results have not been
 impressive

Dosage—The potency of heparin sodium is expressed in units. Ampul solutions keep indefinitely and may be sterilized by boiling or autoclaving at 110 C. for thirty minutes. The substance is inactive orally and is usually injected intravenously. It may be given by single injection or continuous intravenous drip the infusion being adjusted by watching the coagulation time. The clotting time should be maintained between fifteen and twenty minutes. If a chill develops or spontaneous bleeding occurs the drug should be stopped. When the interrupted dose method is employed at intervals of four continuous drip, 100 to 1 000 cc of 5 per cent chloride solution. The flow may be started at about twenty drops per minute.

ABBOTT LABORATORIES

Solution Heparin Sodium 10 cc vials. Each cc. contains 1 000 provisional international units (approximately 10 mg) of heparin sodium. Preserved with phenol 0.5 per cent.

UPJOHN COMPANY

Solution Heparin Sodium 10 cc vials. Each cc contains 10 mg of heparin sodium. Preserved with chlorobutanol 0.5 per cent.

IRON AND IRON COMPOUNDS

Iron is used in medicine: (1) in the form of metallic or elementary iron (reduced iron, U. S. P.); (2) in the ferrous or unoxidized form of combination—responding to tests for ferrous ions (ferrous carbonate in mass of ferrous carbonate and pill of ferrous carbonate, ferrous iodide in syrup of ferrous iodide); (3) in the trivalent or oxidized form, the ferric compounds—responding to tests for ferric ions (ferric chloride in tincture of ferric chloride); and (4) in the form of complex compounds of iron.

Complex (masked or nonionic) iron compounds are those compounds of iron whose solutions do not respond to the ordinary tests for ferrous or ferric ions because in them the iron is part of a radical. Complex compounds of iron do not have the

treatment with strong acids or with alkalis. The complex iron compounds occurring naturally in animal and vegetable tissues (which are often termed food irons) belong generally to the more resistant class, while the complex iron compounds pro-

directly are classed as inorganic iron, whatever their acid radicals may be, and that true iron albuminate and iron peptonate are inorganic iron compounds.)

Actions and Uses.—Solutions of ferric iron are used externally as styptics. Tincture of ferric chloride is an astringent and is used in applications to the throat. The principal use of iron, however, is in the treatment of anemia and chlorosis. For this purpose, the ferrous salts are usually preferred to the ferric salts, as they do not turb the stomach.

are not decomposed by gastric acid, and are void of gastric effects; but, on the other hand, it has been claimed that certain hemoglobin-like compounds escape absorption altogether. Bunge supposed that only "organic iron" could be absorbed and assimilated by the body, the reputed action of inorganic iron being altogether indirect and due to its local effect on the alimentary canal. This theory was modified by Abderhalden to the effect

that inorganic iron while it could not be converted into hemoglobin nevertheless stimulated the conversion of organic iron. Later work (Tartakowski) however proves that inorganic iron is assimilated and converted into hemoglobin and it is in fact therapeutically more effective than natural complex iron compounds. Whipple and his co workers have shown that ferrous carbonate (in the form of Bland's Pills) aids recovery from the anemia of repeated hemorrhages. Starkenstein (Heffner Heubner Handbuch der experimentelle Pharmakologie) reports that Reuman has shown that ferrous salts are effective in bringing about a reticulocyte response, hemoglobin and red blood cell increase in much smaller amounts than the ferric salts. 100 mg of iron as ferrous salts daily were shown to be effective. A difference exists between the different iron preparations in their local irritant and astringent action which is absent in most of the complex iron compounds. These local actions may be desirable in some cases and undesirable in others. This should mainly determine the selection of the particular iron preparation most suitable for each patient. Suitable diet (especially liver kidney meat and spinach) is sometimes more effective than the iron preparations presumably by the cooperation of other factors for in pernicious anemia liver extract that is practically iron free is equally active.

Simple Iron Salts

FERROUS LACTATE.—*Iron Lactate*— $\text{Fe}(\text{C}_3\text{H}_5\text{O}_3)_2 \cdot 3\text{H}_2\text{O}$ —The ferrous salt of lactic acid. The salt contains approximately 19 per cent of metallic iron.

For tests and standards see Section B.

Actions and Uses—Ferrous lactate is a mild chalybeate which because of its feeble taste may be taken without difficulty.

Dosage—From 60 mg to 1.3 Gm. Owing to its liability to oxidation it is best prescribed in solutions containing much sugar. Syrup dissolves 1 Gm. in 120 Gm.

Complex Iron Salts

FERRIC AMMONIUM CITRATE U S P.—"Contains ferric citrate equivalent to not less than 16.5 per cent and not more than 18.5 per cent of Fe [iron]."—U S P.

For description and standards see the U S Pharmacopeia under Ferric Ammonium Citrate and Ferric Ammonium Citrate Capsules.

Actions and Uses—See general article Iron and Iron Compounds. Ferric ammonium citrate is a hematinic which is practically nonastringent.

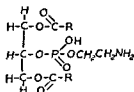
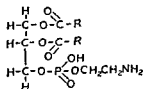
Dosage—1 Gm.

FIBRIN FERMENTS AND THROMBOPLASTIC SUBSTANCES

The clotting of blood (that is, the transformation of the fibrinogen of circulating blood into the insoluble fibrin of blood clot) has been shown to be due to the action of the fibrin ferment (thrombin) on the fibrinogen of the blood. The fibrin ferment of thrombin exists in the blood in the form of its forerunner (prothrombin) which is acted on by the calcium salts and converted into thrombin. Besides calcium salts, however, another factor is necessary. This other factor may be furnished by the breaking down of blood cells or blood platelets or by injured tissues. It has been designated as "zymoplastic" substance by Schmidt, as "thrombokinase" by Morowitz, and as "thromboplastic substance" or "thromboplastin" by Howell.

Actions and Uses.—Preparations containing thromboplastin are said to be useful when applied locally in the treatment of hemorrhage, especially hemorrhage from oozing surfaces, likewise in the treatment of scar tissues, in nosebleed, and in surgery of the bones, glands, nose and throat. Intravenous injection is dangerous, and there is no satisfactory evidence that subcutaneous injection is useful. Preparations should be standardized by testing specimens of blood *in vitro* and should reduce the coagulation time significantly. They should be proved to be sterile. The Council holds that there is no evidence to warrant the internal use of these substances, and further that such use, on account of the danger from anaphylaxis from preparations containing animal products, is likely to be harmful unless proper precautions are taken. The danger is connected with such use; physician determine whether

BRAIN LIPOID.—Impure Cephalin.—Impure Kephalin.—An extract of the brain of the ox, or other mammal, prepared according to the method of Howell as applied in practice by Hirschfelder (*Lancet* 2:542, 1915) and described below. The structural formulas of α - and β -cephalin may be represented, respectively, as follows:



Actions and Uses.—See general article, Fibrin Ferments and Thromboplastic Substances

Dosage.—Brain lipid may be spread on gauze sponges, on

pledgets, or on the tissues themselves; or an emulsion may be prepared by shaking up with physiological solution or sodium chloride and used in the same way or sponged over the tissues.

For use in an office or dispensary, a 5 per cent ethereal solution of brain lipid suffices and can be kept ready for use for some time (several months) in a sterile dropper bottle from

Preparation—

Brain lipid (impure cephalin) is prepared from ox brain which is run through a hashing machine, then covered with 3 volumes of alcohol and agitated two or three times. The excess of alcohol is then poured off

The method of preparation renders it sterile. It can be transferred on a sterile spatula or knife blade to sterile vessels. It retains its activities for several weeks.

(The impurities, largely the lecithins and myelins, do not materially interfere with the activity of the cephalin, but, on the contrary, facilitate its emulsification in isotonic solution of sodium chloride and thus facilitate its intimate miscibility with blood.)

SOLUTION BRAIN EXTRACT.—Solution Thromboplastin-Hess.—An extract of cattle brain in isotonic solution of sodium chloride prepared by the method of Hess (*J. A. M. A.* 56: 558 [Feb. 19] 1916, footnote 2).

Actions and Uses—See general article, Fibrin Ferments and Thromboplastic Substances

Dosage—The solution may be applied directly to the bleeding tissues or sprayed on them, or a sponge or tampon may be immersed in it and then pressed on the bleeding surface.

Preparation—

Cattle brains are obtained fresh from the slaughter house, stripped of their membranes, washed in running water and weighed. They are then

LEDERLE LABORATORIES, DIVISION AMERICAN CYANAMID CO.

Thromboplastin Local: 20 cc. vials.

Clinical Assay.—

The potency of Thromboplastin Local-Lederle is tested as follows: Transfer 0.5 cc. of oxalated blood plasma (0.1 per cent oxalate) to each of a series of tubes, and add 0.2 cc. of Thromboplastin Local-Lederle to each tube. Also transfer 0.5 cc. of oxalated blood plasma to each of a control series of tubes and add 0.2 cc. of physiologic solution of sodium chloride. To each tube (and control) add 0.2 cc. of calcium chloride solution the strength of which is determined by control tests as follows: that dilution of calcium chloride (usually 0.15, 0.25 or 0.5 per cent) is chosen with which the plasma forms solid clots in not less than 20 minutes; Thromboplastin Local-Lederle must cause clotting of the oxalated blood (such as to permit complete inversion of the tubes) within one and one-half minutes; the controls must fail to show clotting at the expiration of 20 to 30 minutes.

THROMBIN: BOVINE ORIGIN

States Public Health Service.

For tests and standards, see Section B.

Actions and Uses.—Thrombin is intended as a hemostatic for topical application to control capillary bleeding in operative procedures. It may be applied as a dry powder or dissolved in sterile, isotonic saline solution. *It should never be injected.*

Dosage.—As a dry powder or in solutions containing 1,000 to 2,000 thrombin units.

PARKE, DAVIS & CO.

Thrombin Topical (Bovine Origin): 5,000 units. Each ampul contains 5,000 units of thrombin, packaged with a 5 cc. vial of sterile isotonic saline solution preserved with phemerol 1:50,000.

LIVER AND STOMACH PREPARATIONS

Whole liver, extracts of liver and dried stomach stimulate maturation of erythrocytes in pernicious anemia and in certain other macrocytic anemias. The Council has accepted only those preparations of liver or stomach which are primarily intended for the treatment of pernicious anemia.

The daily ingestion of 200 to 400 grams of whole liver is effective in inducing a remission in pernicious anemia and in maintaining a normal red blood cell count. Concentrates for oral administration are made from such amounts of liver, but these have lost a certain amount of the original activity of the liver from which they are derived. Extracts suitable for parenteral administration may be prepared from 10 to 15 Gm. of liver and these possess a therapeutic potency equal to that of the larger amounts of liver given by mouth. Similar effects can be produced by 30 to 40 Gm. of desiccated stomach and by combinations of stomach tissue and liver.

For liver extracts and for preparations of stomach the mini-

imum dose is 1 U S P unit per day, or in the case of intramuscular liver preparations multiples of this at longer intervals (e.g. 7 units per week) A U S P unit is the minimum amount which, when given daily to a suitable patient with pernicious anemia in relapse, will cause an adequate hematopoietic response. Inasmuch as material derived from about thirty times as much liver must be given by mouth to produce the same response as when given by injection, it has been necessary to define the "unit" either as an "oral" unit or as an "injectable" unit according to the method of administration of each preparation. For the purpose of standardization (not as a plan to be followed routinely in the treatment of patients) the material is given daily with proper hematopoietic checks to at least three patients whose red blood cell counts are determined before treatment is started, on the day that it is started, and on the seventh day and the fourteenth day of treatment. Daily reticulocyte counts are made during the complete period of the "reticulocyte response." These data are submitted by the manufacturer to the Anti Anemia Preparations Advisory Board of the United States Pharmacopeia which evaluates them and assigns unitage. The board has ruled that at present a strength greater than 15 units per cubic centimeter will not be assigned to a preparation because of the possibility of loss, during the concentration process of unknown factors of value in the treatment of patients with pernicious anemia.

In assigning units to preparations of liver extract or other anti anemia preparations the following points are considered by the board in connection with other available data from therapeutic tests conducted in the manner specified.

- 1 The character and degree of the reticulocyte response.
- 2 Rate of increase of red blood cells
- 3 Clinical factors modifying these responses
- 4 Efficiency of the method of manufacture in preserving the potency of the product.
- 5 The following figures are especially useful to the board in assigning unitage

Initial Red Blood Cell Count (Millions per Cubic Millimeter)	Peak of Reticulocyte Curve (per Cent)
10	41
15	29
20	16
25	11
30	5

These figures are not to be considered as "standards" inasmuch as modifying factors, in each individual patient, may change the interpretation of the type and degree of the response. Under some circumstances a higher or lower response would be expected, making the figures in the table inadequate to express the "normal" for every patient. The ideal test patient should

have a red blood cell count between 1 and 2.5 million per cubic millimeter, and should not have received anti-anemic medication or blood transfusion during the previous month. Infection, marked neurological involvement, extensive arteriosclerosis, severe diarrhea, vomiting or marked gastrointestinal complications are factors which must be taken into account in evaluating the response.

The Council requires that all submitted preparations designed for use in the treatment of pernicious anemia be manufactured by a satisfactory method and that they be labeled with a statement of the number of cubic centimeters or grams of material which constitute an "oral" or "injectable" unit as the case may be. The labeling must also conform to the requirements of the Food & Drug Administration.

FOLIC ACID (See under Folic Acid Preparations).

LIVER - STOMACH CONCENTRATE. — Extralin (LILLY).—Liver with Stomach is a brownish powder resulting from mixing a concentrated water solution of mammalian liver with minced fresh hog stomach tissue. The fraction of liver employed contains that 70 per cent alcohol l per cent alcohol by product is dried und oral administration of 6 Gm. has been found to produce the standard reticulocyte response defined as 1 U. S. P. unit (oral) when assayed in cases of pernicious anemia as required by the Council.

Actions and Uses.—Extralin is proposed for use in the oral treatment of pernicious anemia. See general article, Liver and Stomach Preparations.

Dosage.—For cases of pernicious anemia in relapse, an initial dosage of 2 Gm. (four pulvules) three times daily is suggested; 1.5 Gm. (three pulvules) three times daily constitutes an adequate maintenance dose for most cases. The amount necessary for maintenance varies with different individuals and can be determined only after repeated examinations.

Preparation—

An extract containing the Cohn fraction D is prepared by grinding mammalian livers into water, adjusting the mixture to the iso-electric point (approximately pH 5 to pH 6), and heating to about 80 C. to coagulate protein; this is stirred for thirty minutes and filtered; the filtrate is reduced under vacuum to small volume. This extract is then admixed with finely minced fresh hog stomachs or fresh hog stomach linings. The hydrogen ion concentration is adjusted to approximately pH 5 and the mixture allowed to interact or digest for about two hours at 37.5 C. It is then spread out in a thin layer on pans and dried under vacuum. The dried product is removed from the drier and ground, then extracted with petroleum ether to remove fat. This is dried under vacuum and ground to the proper fineness. The proportions used are such that there is represented in the finished product two to four parts of original liver to one part of original stomach tissue material.

ELI LILLY AND COMPANY

Pulvules Extralin 0.5 Gm Twelve pulvules supply the equivalent of 1 U S P oral unit of liver

U S patent 1,894,247 (Jan. 10 1933 exp res 1950) U S trademark 290 233

POWDERED STOMACH U S P—Dried Stomach—

The dried and powdered defatted wall of the stomach of the hog *Sus scrofa* Linné var *domesticus* Gray (Fam. Suidæ). It contains factors which cause an increase in the number of red blood corpuscles in the blood of persons suffering from pernicious anemia. The activity is readily destroyed when the preparation is suspended in hot liquid. The approximate anti-anemic potency of Powdered Stomach in pernicious anemia is expressed in U S P Units (oral). Powdered Stomach conforms to all other provisions outlined under *Anti anemia Preparations*—U S P

For descriptions and standards see U S Pharmacopeia under Stomach Powdered

Actions and Uses—Dried stomach is used in the treatment of pernicious anemia. See general article Liver and Stomach Preparations

Dosage—The average daily dose should not be less than the amount required to furnish 1 U S P oral unit. Larger doses may be necessary in relapse and in severe or complicated cases. The required doses may be administered in a half glassful of water, milk or fruit juice.

PARKE DAVIS & COMPANY

Ventriculin 100 Gm and 500 Gm bottles Dried stomach 40 grams of material prepared by the method employed in producing the contents of this bottle constitutes 1 U S P unit (oral)

U S patent 1,937,133 U S trademark 270 811

Hormones and Synthetic Substitutes

This chapter includes substances that are internally secreted by particular organs whence they are carried by blood or lymph to other organs for the control of growth or activity. Such substances are called endocrine secretions or hormones. Included

on Autonomic Drugs.

ADRENALS Adrenal Cortex

The cortex of the adrenal gland is essential for life. Adrenalectomized animals die in a few days. During the acute stages of adrenal insufficiency, occurring in disease or as the result of experimental procedures in animals, conditions commonly

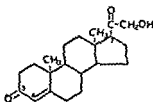
and retention of potassium in most species, loss of carbohydrate reserves with hypoglycemia and retention of nitrogenous products in the blood. Injections of suitable extracts of adrenal cortex which contain more even moribund animals than long as the injections are ride and water are administered concurrently.

Extracts of the adrenal cortex contain several potent substances which influence to a variable degree electrolyte, water or ani ce see...

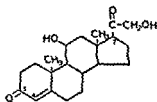
Crystalline compounds have been isolated from the cortex which are capable of maintaining the life of adrenalectomized animals and restoring toward normal the metabolic conditions induced by adrenal insufficiency. These compounds are steroids. The most potent of them are those whose structural formulas are shown below, i.e., desoxycorticosterone (A), corticosterone (B), dehydrocorticosterone (C) and 11-dehydro-17-hydroxycorticosterone (D). Many other steroids have been isolated from

this tissue, but most of these have little known physiologic activity.

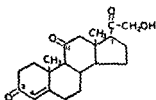
The chemical structure of the cortical steroids is closely related to that of the sex hormones, in fact, some of the cortical steroids have estrogenic or androgenic properties and, in certain



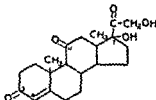
(A)



(B)



(C)



(D)

abnormal conditions of the cortex, large amounts of estrogens

Adrenal cortex extracts have been assayed in many ways. There are advantages to each of the various methods, but it appears that the maintenance of life in the adrenalectomized animal is the most significant measure of activity for such

By these methods the activity of adrenal cortex preparations is expressed in terms of dog units for uniformity of labeled potency. An alternate assay method using adrenalectomized rats according to the procedure of Carl and Kuizenga (*Am. J. Physiol.* 117: 678, 1936) may also be employed and the results transposed in terms of dog units, provided sufficient data are pre-

Desoxycorticosterone, one of the components of adrenal cortex but which is prepared synthetically, is capable of maintaining life in adrenalectomized animals. Desoxycorticosterone differs from extracts of the adrenal cortex in being even more inactive by mouth and in being chiefly concerned with salt and water metabolism. The adrenal cortex has other activities such as a role in the regulation of carbohydrate, fat and protein metabolism.

ADRENAL CORTEX EXTRACT.—An extract of adrenal glands, from domesticated animals used as food in man, containing the cortical steroids essential for the maintenance of life in adrenalectomized animals. Only traces of epinephrine are present.

Actions and Uses.—Although the extract is active by mouth, this method of administration for therapeutic purposes is not to be depended upon. The usual methods of administration are subcutaneous, intramuscular or intravenous injection. The extract is of value in the treatment of Addison's disease or of adrenal insufficiency of other types, and in surgical procedures involving the adrenal cortex when prophylactic measures are needed to prevent the development of temporary adrenal insufficiency. There is as yet no conclusive proof of the value of the extract in the so-called borderline cases of adrenal insufficiency.

For therapeutic purposes varies
l insufficiency, the con-
ection or other compli-
cations, and during a crisis
should govern the dosage.
within a few hours may
crisis, while from 500 dog
tution in many cases of
sodium chloride or other
supplementing adrenal cortex extracts.

Preparation.—

Adrenal cortex extract is prepared by the method of Cartland and Kuizenga (*J. Biol. Chem.* 116:57, 1936). Frozen adrenal glands are extracted with chilled acetone and the gland residue removed by filtration. The acetone extract is concentrated in vacuo below 45 C. and the aqueous fraction so obtained is freed of inactive lipid substances by filtration and extraction with petroleum ether. The aqueous fraction is extracted with ethylene dichloride, which removes the adrenal cortex activity, leaving the epinephrine behind in the aqueous phase. Ethylene dichloride is removed in vacuo, and the residue is dissolved in alcohol and partitioned between 70 per cent alcohol and petroleum ether. The 70 per cent alcohol solution is concentrated in vacuo below 45 C., and sodium chloride is added to the aqueous residue to make 0.9 per cent. An inactive precipitate is removed by filtration. Alcohol is added to make 10 per cent, and the solution is sterilized by Berkefeld filtration.

Adrenal cortex extract is assayed biologically according to the Cartland and Kuizenga method (*Am. J. Physiol.* 117:673, 1936). Each cubic centimeter contains not less than 50 dog units (25 rat units) when assayed according to the method of Cartland and Kuizenga. This assay method depends on the maintenance of life in adrenalectomized dogs. The epinephrine content of the extract as determined by the U. S. P. dog blood pressure method is less than 1:200,000.

THE UPJOHN COMPANY

Solution Adrenal Cortex Extract 50 dog units per cc., 10 cc. and 50 cc. vials Each cc. contains not more than 3 mg. of gland extractives having a potency equivalent to 50 dog units when assayed by the Cartland Kuizenga method, an physiological solution of sodium chloride Preserved with alcohol 10 per cent.

U. S. patent 2 053 349 (Sept. 8 1935 expires 1953) and 2 096 342 (Oct. 19, 1937, expires 1954)

LIPO ADRENAL CORTEX.—An oil soluble extract of hog adrenal glands concentrated by fractionation and containing crystalline biologically active constituents of what are considered to be 17 hydroxycorticosterone 11 dehydro-17 hydroxycorticosterone and corticosterone and a noncrystallizable amount of 11-dehydrocorticosterone The extract is practically free of epinephrine It is assayed biologically according to the survival growth method of Cartland and Kuizenga (*Am J Physiol* 117: 678, 1936) and the muscle work test of Ingle (*Endocrinology* 34: 191, 1944)

Actions and Uses.—Lipo adrenal cortex is employed for the same indications as Adrenal Cortex Extract but is supplied in oil solution only for intramuscular injection when more prolonged absorption is desired

Dosage.—The dosage varies according to the degree of cortical insufficiency and should be governed by the clinical response In crisis or the presence of infection or other complications as much as 2 or 3 cc. daily may be required while from 1 to 2 cc. daily may be sufficient for maintenance Sodium salts are of definite value to supplement adrenal cortex therapy

It should be borne in mind that lipo adrenal cortex has approximately ten times the cortical activity of adrenal cortex extract, and because it is administered in oil solution it should never be injected intravenously

Preparation.—Lipo adrenal cortex is prepared by a method described by Kuizenga, Wick Ingle, Nelson and Cartland (*J Biol Chem* 147: 561 1943) Frozen hog adrenal glands are extracted with chilled acetone and the gland residue removed by filtration Sufficient water is then added to the acetone extract to make a 60 per cent acetone solution. A liquid fat fraction which separates is extracted with 20 per cent acetone and the combined 60 per cent and 20 per cent acetone extracts are concentrated *in vacuo* to remove the acetone The aqueous solution is then extracted with petroleum ether followed by extraction with ethylene dichloride to obtain the active fraction The ethylene dichloride solution is concentrated *in vacuo* below 40° C. and the residue dissolved in 95 per cent alcohol Residual amounts of fat and cholesterol are removed by extraction of aqueous alcohol solutions with petroleum ether which is done first from 70 per cent ethyl alcohol then from 50 per cent methyl alcohol and finally from 30 per cent methyl alcohol The 30 per cent methanol solution free of petroleum ether soluble material is concentrated to remove alcohol and the cloudy aqueous solu-

tion is extracted with ethyl acetate. Acidic and basic substances are removed by washing the ethyl acetate solution with sodium carbonate, followed by 0.5 N HCl and finally distilled water. The ethyl acetate solution is dried with anhydrous $MgSO_4$. The dry concentrate from ethyl acetate is dissolved in acetone, and the required amount of cottonseed oil and 0.5 per cent chlorobutanol is added. The acetone is completely removed *in vacuo* with a stream of N_2 gas, and the resulting oil solution is sterilized by Seitz filtration.

THE UPJOHN COMPANY

Solution Lipo-Adrenal Cortex: 1 cc. and 5 cc. vials. Each cubic centimeter contains not more than 7.5 mg. of gland extractive solids having a potency of 40 rat units (Survival-Growth) and the equivalent in biologic activity to 2 mg. of 11-dehydro-17-hydroxycorticosterone (Muscle-Work Test) in cottonseed oil. Preserved with chlorobutanol 0.5 per cent.

Adrenal Medulla

(See Epinephrine in Chapter on Autonomic Drugs.)

OVARIES

Sex hormones, as a rule, are closely related chemically. These compounds are also similar in structure to the steroids of the adrenal cortex. They possess, likewise, physiological properties common to each other. For instance, certain androgens possess estrogenic or progestational qualities while progesterone is said to have a slight androgenic activity in laboratory animals. The steroids of the adrenal cortex may account for the virilism, feminism or precocious puberty seen in patients with adrenal cortical tumors.

The ovaries produce internal secretions which are necessary for the proper functioning of the uterus, in particular, for the production of cyclic growth processes of the endometrium and for the development of the decidua; in addition these internal secretions determine cyclic changes in the vagina and cervix and influence the growth of the mammary gland. It is known that in addition to intrinsic factors situated in the ovary itself, hormones given off by the anterior pituitary regulate the growth of the follicles, ovulation, and corpus luteum formation.

The follicle stimulating hormone of the anterior pituitary induces growth of the ovarian follicles. During this period estrogenic hormone is secreted by the follicles (probably from the cells of the theca interna), which evokes certain changes in the accessory organs. The vaginal mucosa thickens and the cells undergo a more intense cornification; the myometrium hypertrophies, while the endometrium changes rather rapidly to the proliferative phase. At this time the duct system of the breast develops to a varying degree. After ovulation the follicle becomes

the pituitary,
into a corpus

which secretes progesterone. In the human the corpus luteum elaborates estrogenic hormone as well. The progestational hormone induces secretory changes in the endometrium preparatory to nidation and stimulates growth of the alveolar breast tissue. Menstruation results when the corpus luteum suddenly ceases to produce progesterone. Estrogen is also low at this time. The intrinsic factors which cause extravasation of blood and tissue fragmentation at the end of the cycle are not yet clear.

Estrogen. The injection of potent estrogenic substances in castrate animals will induce changes in the accessory sex organs which are typical of estrus. Long continued injections, however, induce hypertrophic then metaplastic changes in the uterus, cervix and breast. It is often considered that clinical endometrial hyperplasia, chronic cystic mastitis and fibromyomas are due to long continued estrogen secretion by the ovary.

Estrogenic substance is also responsible for the contractility of the uterus and the sensitivity of the myometrium to oxytocic agents. It has recently been shown that the smooth muscle of the human Fallopian tube is also responsive to estrogenic substance.

The excretion curve of estrogenic substances in the normally menstruating women is irregular and varies extremely from day to day. In general, however, there is at least one peak at the height of follicular activity at ovulation time. Excretion curves in ovarian disorders have not been adequately studied at the present time because of numerous technical difficulties in assays. During pregnancy large amounts of estrogens are excreted in the urine in the form of water soluble conjugate. In pregnant women these are in the form of glucuronides and in pregnant mares in the form of sulfates. Hydrolysis of the urine either by acid or by putrefaction converts the conjugated estrogens into their free forms which are more active physiologically.

Estrogenic substances occur widely in nature, in plants as well as in animals. Estrone (ketohydroxyestrin) and estrinol (trihydroxyestrin) are extracted from pregnancy urine or placenta of humans while several estrogens including estrone, equilin and hippulin are obtained from the urine of pregnant mares. Sows ovaries contain both estrone and estradiol (dihydroxyestrin) but not in sufficient quantities to make them a worthwhile source commercially. Estradiol exists in two stereoisomeric forms—alpha and beta. The alpha estradiol is probably the most potent of all known naturally occurring estrogens; the beta form is relatively inert. Since estrogens are relatively rapidly destroyed in the animal body, several estrogen compounds which are absorbed slowly from the site of injection may be more efficient. Fatty acid esters of the estrogens (benzoate, acetate, propionate, palmitate) have therefore been prepared to meet this purpose.

Estrogens are used either orally, intravaginally or by hypodermic injection of a solution in oil or a colloidal suspension in an aqueous solvent. Estrone and estradiol lose considerable activity when taken orally. When estrone is administered in the form of its sulfate it appears to retain a greater amount of its

potency. Several estrogenic compounds have been prepared which lose relatively little potency when administered orally.

Besides crystalline estrogens, preparations of highly purified but noncrystalline estrogens are available. These are usually extracted from the urine of pregnant women or pregnant mares; the estrogenic activity of such extracts is due almost entirely to estrone. The Council has coined the term Solution of Estrogens for such preparations.

... enormous amount of clinical research with ... therapeutic results have been ... inite and consistently reli- ... a relatively small number of conditions. ... could be considered unscientific or in the experimental stage of therapy.

Estrogens are carcinogenic when administered experimentally to animals which have an inherited sensitivity to the development of mammary carcinoma. Many clinicians believe that estrogens are therefore contraindicated in the treatment of women who have a familial or personal history of mammary or genital malignancy. However, the current clinical observations on the use of estrogens in treatment of inoperable breast ... A limited palliative effect may be ... rs, with breast cancer

... considerable variety of ... trogens. These include ... use syndrome, natural ... vulvae, and pruritus ... ficiently small doses of ... motor symptoms of the ... l or vaginal epithelial ... ent of hypogenitalism

inhibit production of ... pituitary. This result requires very large doses. For a ... it was thought that large doses of estrogen inhibited lactation ... immediate ... therapy ... f breasts especially

It has ... inged or ... excessive ... "bleeding" ... by brief ... is con- ... sidered s ... m from ... bleeding ... he cause

of the flowing. The subsequent administration of ... lences of estrogenic substances and progesterone to reestablish cycles of flowing is a possible method of alleviating a condition which is widely believed to result from deficiency of one or both of the ovarian hormones.

Estrogenic materials have been reported to act together with

or as a substitute for castration in the palliation of the local discomforts from prostatic carcinoma and its metastases. The action is apparently not curative but may persist for a number of months.

children, except possibly in cases which are refractory to penicillin.

Progesterone The hormone of the corpus luteum—induces secretory changes of the endometrium, stimulates growth of the mammary alveolar tissue and relaxes the uterine smooth muscle. It is essential for nidation of the ovum and the maintenance of pregnancy. During gestation the ovary elaborates progesterone only through the third month after which the placenta is responsible for its elaboration. Progesterone is not excreted as such, but in the form of pregnandiol glycuronide, and is found in the urine of pregnancy, or during the corpus luteum phase of the normal cycle. Studies on habitual abortion have revealed that pregnandiol excreted in the urine may be abnormally low at about the hundredth day of gestation, indicating an insufficiency of progesterone. It has been calculated that the administration of 10 mg to 50 mg of progesterone daily may be required to bring the pregnandiol level to normal.

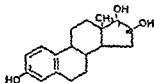
when administered . . . It is crystalline . . . increasing evidence . . . value at the present time.

Commercial preparations of progesterone are either extracts of animal ovaries or the pure compound prepared synthetically. At one time there was considerable enthusiasm over the thera-

or any preparation of this principle

Natural Estrogens

ESTRIOL —Theclol — $C_{18}H_{24}O_3$ —3,16,17 trihydroxy- Δ -13,5 estratriene. A crystalline estrogenic steroid isolated from the urine of pregnancy. The structural formula may be represented as follows



For tests and standards, see Section B.

Actions and Uses.—Estriol is used orally for the same conditions for which estrogenic substances are employed and its contraindications are similar to those of other estrogen. Estriol is much less actively estrogenic than estrone when injected. See general article under Estrogen.

Dosage.—Orally from 0.06 to 0.12 mg. from one to four times a day, alone or as supplement to parenteral therapy.

Estriol is manufactured under license from St. Louis University under U. S. patents 1,967,350 and 1,967,351 (July 24, 1934; expire 1951).

ARNOTT LABORATORIES

Capsules Estriol: 0.12 mg. and 0.24 mg.

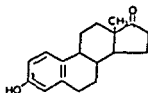
ELI LILLY AND COMPANY

Pulvules Estriol: 0.06 mg., 0.12 mg. and 0.24 mg.

PARKE, DAVIS & COMPANY

Kapsels Theelin: 0.24 mg.

ESTRONE-U. S. P.—Theelin. The structural formula may be represented as follows.



For description and standards see the U. S. Pharmacopeia under Estrone.

Actions and Uses.—Estrone (theelin) is used for the same conditions for which estrogenic substances are employed and its contraindications are similar to those for other estrogens. See general article under Estrogen.

Dosage.—In disturbances of the menopause 0.2 mg. (2,000 I. U.) to 1.0 mg. (10,000 I. U.) injected intramuscularly one or more times weekly depending on the response of the patient. After producing relief, dosage may be lowered to a maintenance level. As much as 50 mg. (50,000 I. U.) per week may be required in resistant cases of kraurosis vulvae. Estrone suppositories are valuable adjuncts in the treatment of senile vaginitis.

Occasionally a considerable amount of uterine bleeding occurs in menopausal women following large doses of estrone. This may be quite alarming at times and it is, therefore, advisable to reduce the dose of estrone as soon as feasible.

Estrone is effective by mouth if the dosage is adequate.

Estrone is manufactured under license from St. Louis University under U. S. patents 1,967,350 and 1,967,351 (July 24, 1934; expire 1951).

ABBOTT LABORATORIES

Solution Estrone in Oil 0.2 mg (2000 I U) 0.5 mg (5000 I U), and 1 mg (10000 I U) per cc in peanut oil 1 cc. ampuls

Solution Estrone in Oil 1 mg (10000 I U) per cc in peanut oil 10 cc. vials Preserved with chlorobutanol 0.5 per cent.

Aqueous Suspension Estrone 2 mg (20000 I U) per cc 1 cc. ampuls Each cc contains estrone crystals 2 mg in aqueous suspension with isotonic sodium chloride solution

Aqueous Suspension Estrone 1 mg (10000 I U) and 5 mg (50000 I U) per cc ampuls Each cc. contains estrone crystals in aqueous suspension with isotonic sodium chloride solution, stabilized with acacia

Vaginal Suppositories Estrone 0.2 mg (2000 I U) in a glycerogelatin base

ELI LILLY AND COMPANY

Aqueous Suspension Estrone 1 mg 2 mg 5 mg per cc 1 cc. ampuls

Solution Estrone in Oil 0.1 mg (1000 I U) 0.2 mg (2000 I U) 0.5 mg (5000 I U) and 1 mg (10000 I U) per cc in sesame oil 1 cc ampuls

Vaginal Suppositories Estrone 0.2 mg (2000 I U) in a glycerine base.

PARKE DAVIS & COMPANY

Solution Theelin in Oil 0.1 mg (1000 I U) 0.2 mg (2000 I U) 0.5 mg (5000 I U) and 1 mg (10000 I U) per cc in peanut oil 1 cc ampuls 1 mg (10000 I U) in peanut oil 10 cc vials

Aqueous Suspension Theelin 1 mg (10000 I U) 2 mg (20000 I U) and 5 mg (50000 I U) 1 cc ampuls

Vaginal Suppositories Theelin 0.2 mg (2000 I U) in glycerogelatin base

ESTROGENIC SUBSTANCES (WATER INSOLUBLE) — Amniotin (SQUIBB) — Plestrin (HARPOUR) — Highly concentrated amorphous or crystalline preparations of estrone (ketohydroxyestrin) together with a small varying amount of other estrogenic phenolic ketones extracted from the urine of pregnant mares

Actions and Uses—Estrogenic substances are used for the same condition for which all estrogens are employed and their contraindications are similar See the general article under Estrogen

Dosage.—From 2,000 to 20,000 international units injected one or more times weekly depending on the response of the patient. After relief has been produced, dosage may be lowered to a maintenance level. As much as 15,000 international units per week may be required in resistant cases of kraurosis vulvae. Suppositories of estrogenic substances are valuable adjuncts in the treatment of senile vaginitis.

Occasionally a considerable amount of uterine bleeding occurs in menopausal women following large doses of any estrogenic substance. This may be quite alarming at times and it is therefore suggested that the dose be reduced as soon as feasible.

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Preparation.—

[illegible]

This residue is further purified by high vacuum fractional distillation. The resulting residue is dissolved in sterile vegetable oil for hypodermic and oral use and incorporated in a glycerogelatin base for vaginal

AYERST, McKENNA & HARRISON, LTD.

Aqueous Suspension Estrogenic Substances: 10,000 I. U. and 20,000 I. U. per cc., 10 cc. vials; 50,000 I. U. per cc., 5 cc. vials.

Solution Estrogenic Substances in Oil: 10,000, 20,000 and 50,000 I U. per cc. in corn oil, 10 cc. vials Preserved with chlorobutanol 0.5 per cent.

BARRY BIOLOGICAL LABORATORY, DIVISION OF BARRY LABORATORIES, INC.

TORIES, INC.

Oil: 10,000 I. U. per cc.
vials. Preserved with

BIORGANIC LABORATORIES, INC.

Estrogenic Substances: Bulk.

GEORGE A. BREEDY & COMPANY INC.

Solution Estrogenic Substances in Oil 10 000 I U per cc. in sesame oil 1 cc. ampuls and 10 cc. and 30 cc. vials, 20 000 I U per cc. in sesame oil 10 cc. vials Preserved with chlorobutanol 0.3 per cent.

BRISTOL LABORATORIES INC.

Solution Estrogenic Substances in Oil with Benzyl Alcohol 3% 2 000 I U, 5 000 I U, 10 000 I U and 20 000 I U per cc. in sesame oil 1 cc. ampuls and 10 cc. and 30 cc. vials

COLL CHEMICAL CO.

Aqueous Suspension Estrogenic Substances 20 000 I U per cc., 10 cc. vials Preserved with chlorobutanol 0.5 per cent

Solution Estrogenic Substances in Oil 2 000 and 5 000 I U per cc. in peanut oil 1 cc. ampuls 10 000 I U per cc. in peanut oil 1 cc. ampuls and 10 cc. vials.

ENDO PRODUCTS INC.

Aqueous Suspension Estromone 20 000 I U per cc., 1 cc. ampuls and 5 cc. and 10 cc. vials Preserved with phenol 0.5 per cent and tri isopropanolamine 0.5 per cent in solution sodium chloride 0.9 per cent

Solution Estromone in Oil 2 000 I U, 5 000 I U, 10 000 I U and 20 000 I U per cc. in sesame oil 1 cc. ampuls and 10 and 25 cc. vials The 10 cc. and 25 cc. vials are preserved with chlorobutanol 0.5 per cent.

Tablets Estromone 1 000 I U, 2 000 I U and 4 000 I U

U S trademark 345 724 May 4 1937

FORBES LABORATORIES

Solution Estrogenic Substances in Oil 10 000 I U per cc. in sesame oil, 1 cc. ampuls 10 cc. and 30 cc. vials 20 000 I U per cc. in sesame oil 1 cc. ampuls and 10 cc. and 20 cc. vials Preserved with chlorobutanol 0.5 per cent

HARROWER LABORATORY INC.

Solution Plestrin in Oil 10 000 I U and 25 000 I U per cc. in sesame oil 1 cc. ampuls 10 cc. and 30 cc. vials Preserved with chlorobutanol 0.5 per cent

U S trademark 233 746

KREMER'S URBAN CO.

Aqueous Suspension Estrugenone with Benzyl Alcohol 2% 50 000 I U per cc. 5 cc. vials 20 000 I U per cc. 1 cc. ampuls and 5 cc. vials

Solution Estrugenone in Oil 2 000 I U per cc. in sesame oil 1 cc. ampuls and 30 cc. vials 10 000 I U per cc. in sesame oil 1 cc. ampuls and 10 cc. vials and 20 000 I U per cc. in

sesame oil, 10 cc. vials. Preserved with chlorobutanol 0.5 per cent.

U. S. trademark 377,549.

LAKESIDE LABORATORIES, INC.

Aqueous Suspension Estrogenic Substances: 20,000 I. U. per cc. in isotonic solution of sodium chloride, 1 cc. ampuls and 5 cc. vials. Preserved with n-butyl p-hydroxybenzoate 0.015 per cent.

Solution Estrogens in Oil: 2,000 I. U., 5,000 I. U., 10,000 I. U. and 20,000 I. U. per cc. in sesame oil, 1 cc. ampuls; 20,000 I. U. per cc. in sesame oil, 10 cc. vials; 10,000 I. U. per cc. in sesame oil, 15 cc. vials. Preserved with chlorobutanol 0.3 per cent.

LINCOLN LABORATORIES, INC.

Aqueous Suspension Estrogenic Substances: 10,000 I. U. and 20,000 I. U. per cc., 1 cc. ampuls; 50,000 I. U. per cc., 5 cc. vials; 10,000 I. U. and 20,000 I. U. per cc. 15 cc. vials, suspended in isotonic sodium chloride solution containing 2 per cent. pectin. 0.1 per cent pectin agents Preserved

Solution Estrogenic Substances in Oil with Benzyl Alcohol 2%: 5,000 I. U., 10,000 I. U. and 20,000 I. U. per cc. in sesame oil, 1 cc. ampuls and 15 cc. vials. Preserved with chlorobutanol 0.5 per cent.

E. S. MILLER LABORATORIES, INC.

Solution Estrogenic Substances in Oil: 5,000 I. U. and 10,000 I. U. per cc. in vegetable oil, 1 cc. ampuls and 10 cc. and 30 cc. vials; 20,000 I. U. per cc. in vegetable oil, 10 cc. and 30 cc. vials, with benzocaine 2 per cent. Preserved with cresol 0.5 per cent.

THE NATIONAL DRUG CO

Solution Estronat in Oil: 5,000 I. U. per cc. in corn oil, 10 cc. Injectosols, 10,000 I. U. per cc. in corn oil, 1 cc. ampuls, 10 cc. and 25 cc. Injectosols, and 20,000 I. U. per cc. in corn oil, 10 cc. and 25 cc. Injectosols. Preserved with chlorobutanol 0.5 per cent

REED & CARNICK

Aqueous Suspension Estrogenic Substances: 20,000 I. U. per cc., 5 cc. and 10 cc. vials. Preserved with chlorobutanol 0.50 per cent.

Solution Estrogenic Substances in Oil: 2,000 I. U., 6,000 I. U., 10,000 I. U., and 25,000 I. U. per cc. in peanut oil. Preserved with chlorobutanol 0.5 per cent.

Tablets Estrogenic Substances: 1,000 I U. and 5,000 I U.

SHARP & DOHME, INC.

Solution Estrogenic Substances in Oil: 2,000 I U., 5,000 I U. and 10,000 I U per cc in peanut oil, 1 cc ampuls

SMITH-DORSEY COMPANY

Solution Estrogenic Substances in Oil with Benzyl Alcohol 3%: 5,000 I U., 10,000 I U and 20,000 I U per cc. in persic oil, 1 cc ampuls, 10,000 I U and 20,000 I U per cc in persic oil, 10 cc ampul vials

Solution Estrogenic Substances in Oil with Benzyl Alcohol 3%: 2,000 I U 5,000 I U and 10,000 I U per cc. in sesame oil, 1 cc ampuls 10,000 I U and 20,000 I U per cc. in sesame oil, 10 cc ampuls Preserved with benzyl alcohol 3 per cent

Capsules Estrone I U. per cc in isotonic sodium chloride suspension, 1 cc. Dual syringe cartridges Preserved with chlorobutanol 0.5 per cent

Aqueous Suspension Estrusol: 20,000 I U per cc. in isotonic sodium chloride suspension, 1 cc. Dual syringe cartridges Preserved with chlorobutanol 0.5 per cent.

Solution Estrusol in Oil: 2,000 I U., 5,000 I U and 10,000 I U per cc in peanut oil, 1 cc. ampuls, 2,000 I U and 10,000 I U per cc. in peanut oil, 15 cc. vials. Preserved with chlorobutanol 0.5 per cent.

Solution Estrusol in Oil with Benzyl Alcohol 3%: 20,000 I U per cc in peanut oil, 1 cc ampuls, and 5 cc and 15 cc vials

Capsules Estrone I U. carbolic

E. R. Squibb & Sons

Capsules Amniotin. 1,000 I U., 2,000 I U., 4,000 I U and 10,000 I U

Pessaries Amniotin: 2,000 I U and 5,000 I U Each pessary contains sufficient estrogenic substances (water insoluble) in corn oil to provide the stated unitage expressed in terms of estrone, enclosed in a soft gelatin capsule for use as a vaginal suppository

Solution Amniotin in Oil: 2,000 I U., 5,000 I U., 10,000 I U. and 20,000 I U per cc in corn oil, 1 cc. ampuls, 10,000

I. U. and 20,000 I. U. per cc. in corn oil, 10 cc. vials; 2,000 I. U. per cc. in corn oil, 20 cc. vials.

U. S. trademark 318,536.

WARREN-TEED PRODUCTS COMPANY

Solution Estrovarin in Oil: 10,000 I. U. per cc. in sesame oil, 1 cc. ampuls and 15 cc. vials. Preserved with chlorobutanol 0.5 per cent.

OLU-

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water

soluble, conjugated forms of the mixed estrogens obtained from the urine of pregnant mares.

The principal estrogen present in estrogenic substances (water soluble) is sodium estrone sulfate. Varying small amounts of other equine estrogens and relatively large quantities of non-estrogenic material are also present in the mixture. The total estrogenic potency of the preparation is expressed in terms of an equivalent quantity of sodium estrone sulfate.

Actions and Uses.—Water soluble estrogenic substances are used in the same conditions for which other estrogenic substances are employed and the contraindications are those for other estrogens. See general article under Estrogen.

Dosage.—For the control of menopausal symptoms, 125 mg. is usually sufficient. If after a few days of treatment the response is not satisfactory, the dose may be increased. After symptoms have been brought under control the dosage can usually be reduced. For the treatment of senile vaginitis, kraurosis vulvae and pruritus vulvae, 1.25 to 3.75 mg. daily should be sufficient.

Preparation.—

Estrogenic substances (water soluble) may be prepared in the following manner: To fresh urine from mares pregnant five months or longer, sufficient xylene is added to prevent hydrolysis of conjugated estrogens. The urine is then concentrated under reduced pressure at 40 to 50 C., the pH being maintained at or near neutrality. The urine concentrate is extracted several times with concentrated butyl alcohol. The butyl alcohol extracts are hydroxide, then twice to a small volume and

The concentrate is material has been removed, the acetone solution is concentrated to a small volume. The acetone concentrate is treated with an excess of ether and the precipitate obtained is removed and dried. This precipitate, which varies in color from reddish brown to almost white, is an amorphous, hygroscopic substance, soluble in water, dissolves in alcohol and acetone.

Estrogenic substance from urine of pregnant mares may be purified by a vacuum dryer.

Estrogenic substances (water soluble) are assayed chemically by a modification of the phenol sulfonic acid colorimetric method introduced by Kober and biologically by oral administration to adult ovariectomized rats, using the technic of Kahnt and Dossy. The standard of reference for the chemical assay is the international standard for estrone. This

standard being inapplicable to the biologic assay of conjugated estrogens, in the rat assay biologic variation is controlled by the use of a house standard preparation of conjugated estrogens.

AYERST, McKENNA & HARRISON, LTD

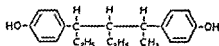
Premarin (*Liquid*): 120 cc. bottles Each 4 cc contains 0.625 mg of estrogenic substances (water soluble) and 12.5 per cent alcohol

Tablets Premarin. 0.63 mg, 0.3 mg, 1.25 mg and 2.5 mg
U. S. trademark 397,925

WYETH, INC.

Tablets Conestron* 1.25 mg, and 0.625 mg
U. S. trademark 422,035

Synthetic Estrogens



For tests and standards, see Section B

daily for four to seven days until the dosage requirement is determined by clinical observation

ml, 10

Tablets Benzestrol 2 mg and 5 mg

SCHIEFFELIN & Co

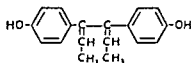
Elixir Benzestrol: 473 cc. bottles Each 4 cc. contains benzestrol 2 mg in a sweetened aromatic elixir containing alcohol 25 per cent

Solution Benzestrol: 5 mg per cc., 10 cc multiple dose vials

Tablets Benzestrol: 0.5 mg., 1.0 mg., 2.0 mg. and 50 mg.

Vaginal Tablets Benzestrol: 0.5 mg.

DIENESTROL.—3,4-bis(*p*-hydroxyphenyl)-2,4-hexadiene.
—The structural formula of dienestrol may be represented as follows:



For tests and standards see Section B.

Actions and Uses.—Dienestrol is used orally for the same conditions for which estrogenic substances are employed, and its contraindications are similar to those of other estrogens.

Dosage.—In the treatment of menopausal symptoms, orally in daily doses of 0.1 to 0.5 mg. for mild to moderately severe symptoms. In artificially induced climacteric a daily dosage of 0.5 to 1.5 mg. may be necessary.

For suppression of lactation a dose of 0.5 mg. three times a day for the first three days and 0.5 mg. daily thereafter for one week is the dosage usually employed.

RARE CHEMICALS, INC.

Aqueous Suspension Dienestrol: 5 mg. per cc., 10 cc. vials.

Tablets Dienestrol: 0.1 mg. and 0.5 mg.

CARROLL DUNHAM SMITH PHARMACAL CO.

Tablets Dienestrol: 0.1 mg. and 0.5 mg.

WHITE LABORATORIES, INC.

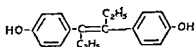
Aqueous Suspension Dienestrol: 5 mg. per cc., 10 cc. vials
Preserved with chlorobutanol 0.5 per cent

Tablets Dienestrol: 0.1 mg. and 0.5 mg.

U. S. patent applied for

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For description and standards see the U. S. Pharmacopeia under Diethylstilbestrol, Diethylstilbestrol Capsules, Diethylstilbestrol Injection and Diethylstilbestrol Tablets.

Actions and Uses—Dodds and his co workers, after extensive experimentation with synthetic substances, recognized the estrogenic activity of the stilbene compounds. Diethylstilbestrol is the

blood fat and calcium in bone induces uterine bleeding in castrate animals and human beings and suppresses ovulation as well as inhibits the secretion of various factors of the anterior pituitary gland, resulting in stunting of growth inhibition of

diethylstilbestrol have been devised, such as fatty acid esters and a number of ethers for increasing the estrogenic efficiency of this substance. These are at present the subject of clinical and physiologic investigations. Diethylstilbestrol possesses the advantage of being highly active by mouth as well as parenterally. The ratio of potency between oral and parenteral administration varies in the hands of different investigators from 1:2 to 1:5 in the human being as well as in rodents. In the therapeutic use of diethylstilbestrol there may be a significant incidence of side reactions the most common of these being nausea, vomiting and headache. It has been considered that these were the result of tissue damage, but no evidence has

pounds, which are slowly absorbed from the site of administration.

Diethylstilbestrol is used for the same conditions for which estrogenic substances are employed and the contraindications are those of the natural estrogens. See general article under Estrogen.

Dosage—The average therapeutic dose for the treatment of menopausal symptoms is 0.5 to 1.0 mg. daily by mouth although it is advised to start with smaller doses for patients who tend to develop disagreeable symptoms. For the suppression of lacta-

tion 5 mg. once or twice daily for a total of from two to four days has been recommended. Courses of therapy with periods of a few weeks of no treatment are recommended by some authorities. Injection of similar quantities of diethylstilbestrol in oil solution are administered one or more times weekly. Ointment or suppositories containing this material may be used for topical applications in the treatment of vulvar and vaginal conditions. In prostatic carcinoma, the recommended dosage is 3 mg. daily intramuscularly for several weeks, after which the dosage is gradually reduced to 1 mg. daily.

ABBOTT LABORATORIES

Solution Diethylstilbestrol in Oil: 0.5 mg., 1.0 mg. and 5 mg. per cc. in peanut oil, 1 cc. ampuls.

Tablets Diethylstilbestrol: 0.1 mg., 0.25 mg., 0.5 mg., 1 mg. and 5 mg.

Vaginal Suppositories Diethylstilbestrol: 0.5 mg.

AMERICAN PHARMACEUTICAL COMPANY, INC.

Tablets Diethylstilbestrol: 0.5 mg., 1 mg. and 5 mg.

BIO-INTRASOL LABORATORIES, INC.

Solution Diethylstilbestrol in Oil: 1.0 mg. per cc. in sesame oil, 1 cc. ampuls.

COLE CHEMICAL CO.

Tablets Diethylstilbestrol: 1 mg.

Solution Diethylstilbestrol in Oil: 1 mg. per cc. in peanut oil, 1 cc. ampuls.

THE DRUG PRODUCTS CO., INC.

Hyposols Diethylstilbestrol in Oil: 1 mg. and 5 mg. in sesame oil, 1 cc. ampuls.

Hyposols Diethylstilbestrol in Oil: 1 mg. per cc. in sesame oil, 30 cc. vials and 5 mg. per cc. in sesame oil, 10 cc. vials. Preserved with chlorobutanol 0.5 per cent.

Pulvoids Diethylstilbestrol: 0.1 mg. and 1 mg.

ENDO PRODUCTS, INC.

Solution Diethylstilbestrol in Oil: 0.5 mg., 1.0 mg., 2.0 mg. and 5.0 mg. per cc. in sesame oil, 1 cc. ampuls.

ESTRO CHEMICAL CO., INC.

Solution Diethylstilbestrol in Oil: 1 mg., 2 mg., and 5 mg. per cc. in corn oil, 1 cc. ampuls and 30 cc. vials. Preserved with chlorobutanol 0.5 per cent.

THE HARROWER LABORATORIES, INC.

Solution Diethylstilbestrol in Oil 10 mg per cc. in peanut oil 1 cc. ampuls and 50 mg per cc. in peanut oil 10 cc. vials. Preserved with chlorobutanol 0.5 per cent.

KREMER-URBAN Co

Tablets Diethylstilbestrol 1 mg and 5 mg

ELI LILLY AND COMPANY

Solution Diethylstilbestrol in Oil 0.25 mg., 0.5 mg., 1 mg and 5 mg per cc. in cottonseed oil 1 cc. ampuls.

Suppositories Diethylstilbestrol 0.1 and 0.5 mg

Tablets Diethylstilbestrol 0.1 mg., 0.25 mg., 0.5 mg., 1 mg and 5 mg

THE WM S MERRELL COMPANY

Tablets Diethylstilbestrol 10 mg and 0.25 mg

E. S. MILLER LABORATORIES INC.

Solution Diethylstilbestrol in Oil with Benzocaine 2% 0.5 mg per cc. in sesame oil with Benzocaine 2 per cent, 1 cc. ampuls. Preserved with cresol 0.5 per cent

Tablets Diethylstilbestrol 0.1 mg., 0.5 mg and 10 mg

PREMO PHARMACEUTICAL LABORATORIES INC.

Solution Diethylstilbestrol in Oil 0.2 mg., 0.5 mg., 10 mg and 50 mg in peanut oil 1 cc. ampuls.

Tablets Diethylstilbestrol 0.1 mg., 0.5 mg., 10 mg and 50 mg

Vaginal Suppositories Diethylstilbestrol 0.1 mg and 0.5 mg

WILLIAM H ROSEN INC.

Solution Diethylstilbestrol in Oil 1 mg per cc. in peanut oil, 1 cc. ampuls.

Tablets Diethylstilbestrol 0.25 mg 1 mg and 5 mg

CARROLL DUNHAM SMITH PHARMACAL Co.

Solution Diethylstilbestrol in Oil 10 mg per cc. in peanut oil, 1 cc. ampuls.

-Tablets Diethylstilbestrol 0.1 mg., and 50 mg

SMITH DEANER COMPANY

Solution Diethylstilbestrol in Oil 0.5 mg and 1 mg per cc. in peanut oil, 1 cc. ampuls.

Tablets Diethylstilbestrol: 0.5 mg. and 1 mg.

E. R. SOUIER & SONS

Tablets Diethylstilbestrol: 0.25 mg, 0.1 mg, 0.5 mg, 1.0 mg, and 5.0 mg.

THE UNION COMPANY

Perles Diethylstilbestrol: 0.1 mg., 0.25 mg., 0.5 mg., 1.0 mg. and 5.0 mg.

Solution Diethylstilbestrol in Oil: 0.5 mg. and 1.0 mg. per cc. in cottonseed oil, 1 cc. ampuls.

Solution Diethylstilbestrol in Oil: 0.5 mg. per cc. in cottonseed oil, 20 cc. vials

THE VALE CHEMICAL CO., INC.

Tablets Diethylstilbestrol: 0.1 mg., 0.5 mg. and 1.0 mg.

WARREN-TEED PRODUCTS COMPANY

Solution Diethylstilbestrol in Oil: 1 mg. per cc in sesame oil, 15 cc vials. Preserved with chlorobutanol 0.5 per cent

Tablets Diethylstilbestrol: 0.5 mg.

WINTHROP-STEARN'S, INC.

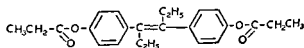
Solution Diethylstilbestrol in Oil: 0.5 mg. and 1 mg. per cc. in sesame oil, 1 cc ampuls.

Suppositories Diethylstilbestrol: 0.1 mg and 0.5 mg.

Tablets Diethylstilbestrol: 0.1 mg., 0.5 mg., 1 mg. and 5 mg.

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structural formula:



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slowly absorbed from the oil depot and causes a lower blood stream concentration, although one of more prolonged duration.

Dosage—Diethylstilbestrol Dipropionate in Oil is administered intramuscularly with the ratio of potency between oral and parenteral administration varying from 1:2 to 1:5. The following average dosages should be modified to meet individual requirements:

Menopausal { from 0.5 to 2 mg. intramuscularly two or
Senile vaginitis { three times a week.

Suppression of lactation—5 mg. intramuscularly once or twice daily for a total of from two to four days.

Carcinoma of the Prostate—3 mg. intramuscularly daily for about ten days.

After a therapeutic effect has been obtained, the dosage should be reduced until the minimum effective dose for maintenance has been established.

THE BULK LANE CHEMICAL COMPANY

Solution Diethylstilbestrol Dipropionate in Oil 10 mg. per cc. in peanut oil 1 cc. ampuls and 10 cc. vials. Preserved with chlorobutanol 0.5 per cent.

Tablets Diethylstilbestrol Dipropionate 0.1 mg., 1.0 mg. and 5.0 mg.

GEORGE A. BROWN & Co., Inc.

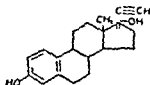
Caplets Diethylstilbestrol Dipropionate 0.2 mg., 0.5 mg., 1.0 mg. and 5.0 mg.

Solution Diethylstilbestrol Dipropionate in Oil 10 mg. per cc. in sesame oil 1 cc. ampuls.

WINTHROP-STEARNS, Inc.

Solution Diethylstilbestrol Dipropionate in Oil 0.5 mg. per cc., 1 mg. per cc. and 5 mg. per cc. in olive oil 1 cc. ampuls.

ETHINYL ESTRADIOL—Ethinyl (SCHERING)—17 ethinyl 3,17-dihydroxy Δ 1,3,5 estratriene—A crystalline synthetic estrogenic derivative of α estradiol possessing the following structural formula:



For tests and standards see Section B.

Ethinyl estradiol may be prepared by the action of potassium

acetylide upon estrone in liquid ammonia, followed by evaporation of the ammonia, solution in water and precipitation with mineral acid. The product is purified by recrystallization from methanol. When assayed biologically in rats by the Allen-Doisy method, ethinyl estradiol exhibits a potency of approximately 100,000 I.U. per milligram.

Actions and Uses.—The ethinyl radicle delays the decomposition of the estradiol molecule in the stomach, intestine, and liver, so that the drug can be given orally; it is one of the most potent estrogens known. In the female it compensates for deficiencies in estrogen production; in the male it opposes some of the actions of the androgens, as in prostatic carcinoma.

Dosage.—In hypo-ovarianism, three 0.05 mg. tablets daily by mouth are stated to be adequate for most patients. At the menopause, one 0.05 mg. tablet per day may be needed at first, but 0.02 mg. per day generally suffice for maintenance.

For functional uterine bleeding (menometrorrhagia) the suggested course consists of three cycles exactly alike. The first cycle begins as soon as the diagnosis is made, and consists of 20 days of treatment, 5 days of latent period, and 5 days of bleeding-episode, making a total of 30 days. From the first to the 15th day the daily treatment is six 0.05 mg. tablets of ethinyl estradiol alone. From the 16th to the 20th day the patient receives a daily intramuscular injection of 5 mg. of progesterone in addition to the daily dose of six 0.05 mg. tablets of ethinyl estradiol. The treatments are then suspended, and after a latent period of about five days the patient generally begins to bleed. Five additional days are allowed for this bleeding-episode, whereupon one begins the second cycle of treatments.

In prostatic carcinoma, the recommended dosage is three 0.05 mg. tablets daily for several weeks, after which the dosage is gradually reduced to one tablet daily. The incidence of side reactions, such as headache, nausea, and vomiting, is found in the same proportion of patients as occurs with other orally active estrogens.

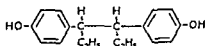
SCHERING CORPORATION

Estinyl (Liquid): 120 cc. and 480 cc. bottles. Each 4 cc. contains ethinyl estradiol 0.03 mg. in syrup of cherry N. F. with 20 per cent alcohol.

Tablets Estinyl: 0.02 mg. and 0.05 mg.

U. S. patents 2,251,939 and 2,265,976. U. S. trademark 398,209.

HEXESTROL.—*Meso-3,4-di-parahydroxyphenyl-n-hexane.* Hexestrol may be represented by the following structural formula:



It may be prepared from anethole in ether solution by (a)

treating with anhydrous hydrogen bromide to form anethole hydrobromide, (b) conversion of the anethole hydrobromide to 3,4-dianisylhexane by means of metallic magnesium, aluminum, copper or zinc turnings and (c) hydrolysis of the 3,4-dianisylhexane to form hexestrol. The product thus obtained may be purified by recrystallization from dilute alcohol.

For tests and standards, see Section B

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Dosage—As is the case with all estrogenic substances, the

tenance dose, or by injection 10 mg in oil three times weekly with similar lowering for maintenance of control. For senile vaginitis and kraurosis vulvae, 2 to 3 mg daily by mouth, or 1 mg in oil three times weekly by injection. For suppression of lactation, 150 mg one to three times daily for two or more days or 150 mg in oil daily for two or more days by injection.

S. E. MASSENGILL CO

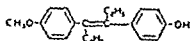
Tablets Hexestrol 3 mg

THE WM S MERRELL COMPANY

Solution Hexestrol in Oil 1 mg and 5 mg per cc in vegetable oil 20 cc vials Preserved with chlorobutanol 0.5 per cent

Tablets Hexestrol 0.2 mg 10 mg and 30 mg

MESTILBOL.—Monomestrol (WALLACE & TIERMAN)—Diethylstilbestrol monomethyl ether—3-*p*-hydroxyphenyl-4-*p*-methoxyphenyl 3-hexene.—*cis*-Diethyl-4-methoxy-4-stilbenol.—Mestilbol may be represented by the following structural formula



ether mixtures.

For tests and standards, see Section B

Actions and Uses.—Mestilbol is used for the same conditions for which estrogenic substances are employed, and the contraindications are essentially the same. Like other estrogens, it must be individualized since each patient presents special problems. Patients undergoing treatment should remain under constant medical supervision. Side effects are rare, but when they do occur they are usually mild, although in a few instances it may be necessary to reduce the dosage temporarily.

Dosage.—The average oral dose for the treatment of menopausal symptoms is 0.5 to 1 mg. daily by mouth, although if necessary 10 to 25 mg. may be given parenterally biweekly. Dosage for atrophic genital disorders such as kraurosis vulvae include 1 to 5 mg. daily by mouth or 25 mg. weekly by parenteral injection; for the prevention of breast engorgement 5 to 10 mg. daily or 25 mg. the first and third days by injection; for suppression of lactation 10 mg. two or three times daily, or 25 mg. daily by injection; for prostatic cancer 2.5 mg. three times daily by mouth. The duration of treatment varies and may last for several months or even two or three years in the treatment of the menopause, a few months for atrophic genital disorders, three to five days for prevention of breast engorgement and suppression of lactation or be continuous for prostatic cancer.

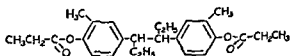
WALLACE & TIERNAN PRODUCTS, INC.

Solution Monomestrol in Oil: 10 mg. and 25 mg. per cc. in sesame oil, 1 cc ampuls.

Tablets Monomestrol: 0.25 mg., 0.5 mg., 10 mg., 2.5 mg. and 50 mg.

U. S. patent 2,385,468 (Sept. 25, 1945; expires 1962) and U. S. trademark 397,572.

PROMETHESTROL DIPROPIONATE.—Meprane Dipropionate (REED & CARRICK).—Dimethylhexestrol dipropionate.—3,4-Bis-(*m*-methyl-*p*-propionoxyphenyl)hexane.—The structural formula of promethestrol dipropionate may be represented as follows.



For tests and standards, see Section B.

Actions and Uses.—Promethestrol Dipropionate is similar in its actions to diethylstilbestrol and other synthetic estrogens. It is used for the same conditions for which estrogenic substances are employed and the contraindications are those of the natural estrogens.

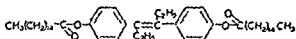
Dosage.—In the menopause, treatment may be started with 1 mg. given three times daily, gradually reducing the dosage to 1 mg. daily. For suppression of lactation, 3 to 5 mg. daily.

REED & CARNICK

Tablets Meprane Dipropionate · 1 mg

U S patent applied for

STILPALMITATE — Diethylstilbestrol dipalmitate — The dipalmitic acid ester of diethylstilbestrol — The structural formula of diethylstilbestrol dipalmitate may be represented as follows



For tests and standards, see Section B

Actions and Uses — The actions and uses of stilpalmitate are essentially those of diethylstilbestrol except that the absorption of stilpalmitate is slower. This delay in absorption permits a more prolonged therapeutic effect and is believed to lessen unpleasant side effects.

The contraindications for this preparation are the same as those for all substances with estrogenic action.

Dosage — Stilpalmitate is given by intramuscular injection only. The usual dose is 5 mg in terms of the diethylstilbestrol content. As with other estrogens, individual patient response will vary considerably as to rapidity of symptom relief and duration of effect. In the treatment of menopausal symptoms

.....

dosage periods will vary from four to twelve weeks.

Lactation may be suppressed during the puerperium by the injection of 10 mg of diethylstilbestrol as the dipalmitate ester on the day of delivery and 5 mg on the first and second post partum days.

Ampuls must be immersed in hot water to dissolve the stilpalmitate, which is insoluble at room temperature. The drug will remain in solution at body temperature.

ABBOTT LABORATORIES

Solution Stilpalmitate in Oil 7 mg and 14 mg per cc in peanut oil 1 cc ampuls

PANCREAS

The pancreas is a gland having in general, two functions: (1) It secretes into the intestine a digestive juice containing the enzymes trypsin, lipase and amylase, (2) it secretes into the blood a hormone, insulin, which regulates the process of carbohydrate metabolism.

When insulin secretion is deficient, or possibly when there is an overproduction of sugar due to other causes, diabetes develops. In this disease the percentage of sugar increases in the blood (hyperglycemia) so that sugar overflows into the urine (glycosuria). The hyperglycemia is associated with a breakdown of the first and last stages in the metabolism of sugar, as revealed, respectively, by failure of glycogen to be deposited in the liver and by failure of the respiratory quotient to become increased when carbohydrate food is ingested. The depression in carbohydrate metabolism may be accompanied by an accumulation of ketone substances (acetone, acetoacetic and oxybutyric acids) with resultant acidosis and, later, coma.

sugar, increased storage as glycogen in the liver and possibly in the muscles is a factor in the result. When the percentage of blood sugar falls below the kidney threshold in the diabetic patient, sugar disappears from the urine. If an overdose of insulin is given, the blood sugar falls to a subnormal level, and characteristic symptoms are observed. The level at which these symptoms occur depends not only on the extent but also on the rate of fall. If the blood sugar has been persistently high and is rapidly reduced, hypoglycemic symptoms may appear at a much higher level of blood sugar than when the fall is slower and more gradual. These symptoms are due to the diminished sugar in the blood, as shown by the fact that they are relieved by the replacement of the sugar by oral or intravenous administration.

Clinical assays conducted on patients with uncomplicated diabetes on certain standard dietary regimens reveal that one insulin unit will on an average promote the metabolism of approximately 1.5 Gm. of dextrose. The physician may, therefore, gage his insulin dose with some precision. To do so, he must know how much dextrose the patient will derive from his food.

The latter may be able to utilize carbohydrate by utilizing insulin injections at regular intervals and must be supplemented by

from glycosuria and good mental and physical vigor for patients with severe diabetes.

There is as yet no positive evidence that treatment with insulin will arrest the diabetic process by restoring the patient's anti-diabetic function. In the severer cases, the evidence now available is against such an assumption. In the milder cases in which insulin has been used, the evidence is difficult of interpretation

because such patients may show very marked improvement in their ability to utilize carbohydrate on dietary regulation and exercise alone

Oral Administration of Pancreatic Preparations—In diabetes, reliance on the oral administration of the pancreatic preparations thus far available has no justification and such practice merits the most vigorous condemnation. Many reputed anti-diabetic pancreatic preparations are on the market with claims that they are effective if taken by mouth. The most widely heralded of them have been subjected to the scrutiny of clinical tests controlled with simultaneous laboratory investigation. None of these thus tested has shown any effect on blood sugar or glycosuria. Completely negative results were obtained when

Insulin Labeling Regulations

Regulations concerning the certification of batches of drugs composed wholly or partly of insulin are presented in the 8 Federal Register 11837 Aug 27 1943. Of special interest to the physician are statements on labeling. Each package must contain on the outside wrapper information on the batch mark strength of the drug in terms of U S P units of insulin per cc., expiration date and the warning: Keep in a cold place. Avoid freezing. The circular or other labeling must contain special information for the guidance of the physician. The outside containers or wrappers must be distinguished by various colors.

Insulin U S P is distinguished by

Yellow if it contains 20 U S P Units of insulin per cubic centimeter

Red if it contains 40 U S P Units of insulin per cubic centimeter

Green if it contains 80 U S P Units of insulin per cubic centimeter

Orange if it contains 100 U S P Units of insulin per cubic centimeter

If the master lot used was in crystalline form the distinguishing colors may be:

Blue and gray or *blue gray* and *yellow* if it contains 20 U S P Units of insulin per cubic centimeter

Red and gray if it contains 40 U S P Units of insulin per cubic centimeter

Green and gray, if it contains 80 U S P Units of insulin per cubic centimeter

Protamine zinc insulin is distinguished by:

Red and white, if it contains 40 U. S. P. Units of insulin per cubic centimeter.

Green and white, if it contains 80 U. S. P. Units of insulin per cubic centimeter.

Globin insulin with zinc is distinguished by:

Red and brown, if it contains 40 U. S. P. Units of insulin per cubic centimeter.

Green and brown, if it contains 80 U. S. P. Units of insulin per cubic centimeter.

Preparations

GLOBIN INSULIN WITH ZINC.—"Globin insulin (with zinc) is a preparation, in a hydrochloric acid medium, of insulin modified by the addition of globin (derived from the hemoglobin of beef blood) and zinc chloride. The quantity of insulin used is such that each cubic centimeter of the finished product contains either 40 or 80 U. S. P. units of insulin. The quantity of globin used (calculated as 60 times its nitrogen content) is not less than 36 mg. and not more than 40 mg. for each 100 U. S. P. units of insulin used. The preparation also contains, for each 100 U. S. P. units of insulin used, not less than 0.25 mg. and not more than 0.35 mg. zinc and not more than 1.50 mg. total nitrogen. The pH of the finished preparation is not less than 3.4 and not more than 3.8. If necessary, either hydrochloric acid or sodium hydroxide may be added to obtain the required pH. The finished preparation also contains not less than 1.30 and not more than 1.70 per cent (W/V) of glycerin and not less than 0.15 per cent and not more than 0.20 per cent (W/V) cresol-U. S. P., or not less than 0.20 per cent and not more than 0.26 per cent (W/V) phenol-U. S. P. The preparation is sterile."—Regulations promulgated Aug. 24, 1943 by the Administrator, Federal Security Agency: Certification of Batches of Drugs Composed Wholly or Partially of Insulin [8 Fed. Reg. 11837 (Aug. 27, 1943)], as amended [10 Fed. Reg. 2904-2905 (Mar. 17, 1945)].

Standards for Globin Insulin with Zinc and the Globin used in its preparation are set forth in the regulations cited.

Actions and Uses.—The effects of globin insulin with zinc are essentially the same as those of insulin (which see) except that the action is intermediate between that following regular insulin and protamine zinc insulin. The period of greatest effect extends from the eighth to the sixteenth hour after injection. This agent whom regulate control and may be used in some patients to replace, wholly or partly, ordinary insulin. It is claimed to be indicated for those patients

who require more than one daily injection of unmodified insulin and for those who cannot be controlled by other forms of insulin or who exhibit a sensitivity to protamine. It is said also to produce fewer local reactions on injection. It is not recommended for the treatment of diabetic coma and should never be administered intravenously. Globin insulin with zinc is quite stable but nevertheless bears on the label an expiration date for usage.

Dosage.—The general principles underlying the administration of this form of insulin are the same as those governing the use of unmodified insulin. It must be administered only by deep subcutaneous injection, not intramuscularly or intravenously. The daily dose required must be determined by a study of the patient. However, a starting dose may be about two thirds to three fourths of the total daily dose of regular insulin. This may be increased slowly as needed. If the patient has been receiving protamine zinc insulin, the globin insulin dosage on the first day should not exceed one half the total dose of all insulin (regular, protamine zinc) received on the previous day. On the next day the dose may be increased to two thirds of the previous total insulin dosage and then slowly adjusted as required.

BURROUGHS WELLCOME & Co., Inc.

Globin Insulin with Zinc 40 and 80 units, 10 cc. vials
Each cc. contains 40 and 80 units of globin insulin with zinc.
Contains cresol 0.18 per cent as a preservative.

U. S. patent 2,161,191 (June 6 1939 expires 1956)

F. R. Squibb & Sons

Globin Insulin with Zinc 40 and 80 units, 10 cc. vials
Each cc. contains 40 and 80 units of globin insulin with zinc respectively. Contains phenol 0.25 per cent as a preservative.

INSULIN INJECTION U. S. P.—Hletin (Lilly)—Insulin—Insulin Hydrochloride.—An acidified solution of the active principle of the pancreas which affects the metabolism of glucose. Insulin Injection when assayed as directed shall possess a potency of not less than 95 per cent and not more than 105 per cent of the potency stated on the label, and the potency shall be expressed in U. S. P. Insulin Units which are equivalent in potency to the Unit declared on the label of the container of the U. S. P. Zinc Insulin Crystals Reference Standard.

"Insulin Injection is so standardized that each cc. contains either 20, 40, 80, or 100 U. S. P. Insulin Units"—U. S. P.

For description and standards see the U. S. Pharmacopeia under Insulin Injection.

Actions and Uses.—Insulin lowers the blood sugar in normal rabbits causing characteristic symptoms when a low level is reached, which symptoms are overcome by the administration of dextrose. It prevents the hyperglycemia due to pique.

asphyxia and epinephrine. It increases the sugar consumption of the isolated mammalian heart. It causes glycogen to be deposited in the liver of diabetic animals fed with carbohydrates, and raises the respiratory quotient of such animals. It affects the metabolism of fat in diabetic animals and causes the acetone bodies to disappear from the urine. It has been demonstrated that the administration of insulin to diabetic dogs and to man in

and the urine remains free of sugar; fat is also burned and as a result, ketone bodies do not appear in the urine and diabetic acidosis and coma are prevented.

The administration of insulin is indicated in cases of diabetes mellitus which cannot be controlled at a satisfactory level by dietetic treatment. In such cases, with proper regulation of the diet, insulin should be administered in such amounts as to prevent glycosuria and a too great hyperglycemia. In some cases the dosage of insulin may be gradually decreased as the body power of utilizing carbohydrate returns toward normal.

Overdosage of insulin is followed by the development of serious symptoms which demand immediate treatment. The patient complains of weakness and fatigue and a feeling of nervousness or tremulousness. This is followed by profuse sweating,

hand. In case of emergency when sterile solution of insulin is not available, a subcutaneous injection of 0.3 cc. to 0.6 cc. of 1 in 1,000 solution of epinephrine may be employed, but this must always be followed by carbohydrates by mouth. The injection of epinephrine must be employed carefully as its action depends on the presence of glycogen, of which there is usually very little in the diabetic organism. Epinephrine should never be employed when the hypoglycemia follows excessive exercise, vomiting or the omission of meals.

Insulin has been used in the treatment of non-diabetic malnutrition with reported increase in appetite and gain in weight. Care is necessary in avoiding symptoms of hypoglycemia.

Insulin has been suggested and used rather extensively in psychopathic hospitals for the purpose of producing hypo-

stable solutions of dextrose for interrupting the hypoglycemic state which is artificially created in these individuals by the administration of insulin

Dosage—Insulin is administered by injection into the loose subcutaneous tissue of the body, usually thirty minutes before meals. There is no average dose of insulin for diabetics; each

trose minus the dextrose excretion. A convenient formula is

$$\frac{\text{Average grams of d glucose excreted}}{5} = \text{sufficient units of insulin to}$$

 render most patients aglycosuric. Usually the daily dose is administered in two equal portions, one before breakfast and

the fasting blood sugar normal but hypoglycemia should be avoided. If patients are not under close observation, half the estimated dose may be used and the dose gradually increased until therapeutic results are obtained. Complications such as infections, may reduce the dextrose tolerance, thus necessitating an increase of insulin dosage

In cases of coma or severe acidosis an initial dose of 30-60

In a small number of cases of diabetes mellitus insulin can be given in small doses to help such patients who have

Dosage of insulin should always be expressed in units rather than in cubic centimeters or minims. The volume of a dose of insulin containing a certain number of units will vary with the strength of the solution which is employed. In general it is advisable to keep the volume per injection at from $\frac{1}{4}$ to $\frac{3}{4}$ cc., choosing the strength of insulin which will give the required number of units in this volume or less.

U. S. patents 1,469,994 (Oct. 9, 1923; expired); 1,470,024 (Oct. 9, 1923; expired) and 1,520,673 (Dec. 23, 1924; expired). Canadian patent 234,336 and 234,337. U. S. trademark 179,174. Canadian trademark 31,646.

ELI LILLY AND COMPANY

Iletin: 40 units and 80 units, 10 cc. vials. Each cc. contains 40 and 80 units insulin respectively.

U. S. trademark 171,971.

SHARP & DOHME, INC.

Insulin: 40 units, 80 units, 100 units, 10 cc. vials. Each cc. contains 40, 80 and 100 units respectively.

Beef pancreas is rendered as free from fat and connective tissue as possible, and extracted with acidulated 60 per cent alcohol. The mixture is centrifugalized and the gland residue reextracted with 60 per cent alcohol. The alcoholic liquid is then concentrated to about one twelfth its original volume. The active substance is then precipitated with ammonium sulfate, and reprecipitated from an alcoholic solution. It is further purified by a method of iso-electric precipitation and is finally dissolved in acid water (pH 2.5). 0.25 per cent phenol is used as preservative and glycerin 1.6 per cent is added in order to attain isotonicity. It is then filtered through a Berkefeld filter and submitted to sterility tests; its potency is determined by the method described under the preceding article, Insulin.

E. R. SQUIBB & SONS

Insulin: 40 units, 80 units, 100 units, 10 cc. vials. Each cc. contains 40, 80 and 100 units respectively.

Insulin Squibb is made by extracting finely ground beef pancreas with acidulated aqueous alcohol and subsequently removing the tissue by centrifuging. The alcoholic solution is concentrated and the insulin is precipitated by ammonium sulfate after the removal of fats. This sulfate precipitate is dissolved in dilute ammonia and impurities removed by alcoholic precipitation. From the above filtrate the insulin is precipitated with ether and redissolved in ammonia. It is then reprecipitated at its iso-electric point pH 4.8-5.2. This nearly pure insulin precipitate is centrifuged and dissolved in acid water which is then passed through a Berkefeld filter and assayed. The finished preparation contains 0.1 per cent phenol as a preservative.

Fresh pancreatic glands of animals, from which fat and connective tissue have been removed, are ground and extracted with $1\frac{1}{2}$ volumes 95 per cent alcohol, containing 0.11 per cent absolute sulfuric acid. The mixture is agitated during two hours and then filtered. The residue is again extracted using an equal volume of 70 per cent alcohol containing 0.11 per cent absolute sulfuric acid. This is filtered and the filtrate added to the first filtrate. The combined filtrates are chilled to 0 C and filtered. The filtrate is concentrated to about one twenty fifth its original volume and filtered, and the filtrate added to 5.3 times its volume of 95 per cent alcohol. This mixture is allowed to stand for several hours, and then filtered, and the filtrate made up to contain 93 per cent alcohol. After standing several days, the precipitate formed is collected and dissolved in distilled water. The insulin preparation is further purified by precipitation at the isoelectric point, the hydrogen ion concentration

being adjusted to approximately pH 4.7, after which the solution is allowed to stand in the icebox. The precipitate formed is dissolved in acidified water (pH 2.5) filtered, reprecipitated and redissolved if necessary for further purification. The solution is then diluted to approximately the desired potency, filtered through a Berkefeld filter, and submitted to standardization and sterility tests. The finished preparation contains 0.2 per cent phenol as a preservative.

PROTAMINE ZINC-INSULIN INJECTION. U. S. P.

—Protamine, Zinc and Iletin (Lilly).—"A suspension, in a buffered water medium, of insulin modified by the addition of zinc chloride and protamine. The protamine is prepared from the sperm or from the mature testes of fish belonging to the genera *Oncorhynchus* Suckley, *Salmo* Linne, or *Trutta*, Jordan and Evermann (Fam. Salmonidae), and conforms to the regulations of the Food and Drug Administration concerning certification of batches of drugs composed wholly or partly of insulin.

"In the preparation of Protamine Zinc Insulin Injection the amount of insulin used is sufficient to provide either 40 or 80 U. S. P. Insulin Units for each cc. of the injection.

"*Note*—Protamine Zinc Insulin Injection differs in its action from that of Insulin Injection both in time of onset and duration. To secure accuracy of dosage the preparation must be brought into uniform suspension by careful shaking before use." U. S. P.

For description and standards see the U. S. Pharmacopeia under Protamine Zinc Insulin Injection.

Actions and Uses.—The effects of protamine zinc insulin are the same as those of insulin (which see), except that the blood-sugar lowering action of unmodified insulin becomes maximal in from two to three hours whereas the blood-sugar lowering action of protamine zinc insulin is prolonged and has its greatest effect in about twelve to twenty-four hours after administration.

Protamine zinc insulin may be used in the case of any patient where regulation of diet is incapable of removing the cardinal objective symptoms of diabetes mellitus, and may replace, wholly or partly, the use of unmodified insulin in the treatment of the patient. In some cases the use of unmodified insulin alone is desirable, in others, protamine zinc insulin alone is indicated, while in others, the use of both preparations gives best results.

In view of the prolonged action of protamine zinc insulin, the chief indications for its use are in those cases where unmodified insulin is unable to provide control without being administered in several doses daily, or is unable to provide adequate control unaccompanied by frequent hypoglycemic reactions, ketosis or evidence of pronounced fluctuations in blood sugar levels. The usefulness of protamine zinc insulin in cases of diabetic coma in diabetes complicated by infection, or in the event of surgical operations has not been definitely established. In such instances therefore the use of protamine zinc insulin to supplant the use of unmodified insulin is not recommended.

Dosage.—The general principles underlying the administration

of protamine zinc insulin are the same as those governing the administration of unmodified insulin (see Insulin Injection).

Protamine zinc insulin is to be injected *only subcutaneously*. In most cases its administration more often than once a day is not required. The initial dose should be from about two-thirds to equal the number of units that would be needed daily to maintain the patient "sugar free" under treatment with unmodified insulin. In some instances glycosuria may follow owing to the slow absorption and consequent delayed action of protamine zinc insulin. Hence on the first few days when protamine zinc insulin is being used, it may be advantageous to administer a separate dose of unmodified insulin. It is usually possible to discontinue the use of unmodified insulin after the first or second day,

fast), or in the evening (one hour before supper or one hour before retiring). Diet must be adjusted with the prolonged blood-sugar-lowering effect of the product in mind, and a redistribution of food among individual meals is usually desirable. In particular, the carbohydrate content of the meal following the injection of protamine zinc insulin may have to be limited in order to avoid *hyperglycemia*. The carbohydrate of the diet not included in this meal is divided between the other meals of the day in such a manner as to prevent *hypoglycemia* at times when the dose of protamine zinc insulin is exerting its greatest effect.

... following administration
... be less obvious
... nsulin, and may
... ..

of one or two
time. In sever
15 to 20 Gm.
lowed later by food.

ELI LILLY AND COMPANY

Protamine Zinc and Iletin: 40 units and 80 units, 10 cc. vials. Each cc. contains 40 and 80 units of protamine zinc insulin respectively.

Iletin is registered under U. S. trademark 171,971.

SHARP & DOHME, INC.

Protamine Zinc Insulin 40 units and 80 units 10 cc. vials Each cc. contains 40 and 80 units of protamine zinc insulin respectively Contains disodium acid phosphate 0.2 per cent, phenol 0.25 per cent as a preservative and glycerin 1.6 per cent for isotonicity

E. R. Squibb & Sons

Protamine Zinc Insulin 40 units and 80 units 10 cc. vials. Each cc. contains 40 and 80 units of protamine zinc insulin respectively

ZINC INSULIN CRYSTALS—Zinc insulin crystals are a crystalline preparation of the active antidiabetic principle of the internal secretion of the islands of Langerhans of the pancreas. The crystals contain a small amount of zinc (not less than 0.45 per cent and not more than 0.9 per cent) which is chemically combined with the active principle. Each milligram of the crystals is equivalent to not less than 22 units of insulin. The product is marketed in the form of crystalline zinc insulin injection.

For tests and standards see Section B

CRYSTALLINE ZINC INSULIN INJECTION—

Insulin Made from Zinc Insulin Crystals—A solution of zinc insulin crystals, a preparation containing the active antidiabetic principle of the pancreas combined with a small amount of zinc (not less than 0.2 and not more than 0.40 mg. per thousand units of active principle in the solution)

Crystalline zinc insulin injection meets the requirements for identity and purity provided in the U. S. P. under Insulin Injection

Actions and Uses—Crystalline zinc insulin injection may be used in the treatment of diabetes mellitus when regulation of diet has been unsatisfactory in control of the disease. Because of its chemical purity solution of zinc insulin crystals is especially indicated for patients who may be expected to exhibit allergic reactions to insulin. Experience has indicated that the occurrence of such reactions may thus be avoided or minimized. Although early clinical observations indicated that the action of crystalline zinc insulin injection as compared with that of insulin may be slightly delayed and somewhat prolonged, further clinical experience has shown that, in patients under careful observation, crystalline zinc insulin injection and insulin may be used interchangeably.

Dosage—The potency of crystalline zinc insulin injection is measured in terms of standard units of insulin. The general principles underlying its administration are the same as those covering the use of insulin, and under ordinary circumstances the two solutions may be regarded as interchangeable. The

crystalline zinc insulin injection is usually best administered subcutaneously fifteen to thirty minutes before a meal. The time and number of the doses and the amount of solution must be de-

tive and sufficient 0.01 normal hydrochloric acid to yield a pH of from 2.5 to 3.5. The biologic activity of the solution is expressed in U. S. P. insulin units per cubic centimeter. Solutions of zinc insulin crystals are stable, provided the storage temperature does not exceed room temperature.

PARATHYROID

Parathyroid preparations for oral administration are made from the dried gland and for subcutaneous administration by extraction of

fication of the lack any conc use of the gland. No proof has been brought forward that the one definite effect that can be referred to the parathyroid gland (maintaining or raising the calcium concentration of the serum) has been produced by parathyroid preparations taken by mouth. To ascribe to the oral administration of parathyroid preparations improvement in conditions that are not definitely known to depend upon parathyroid disease, or deficiency, is illogical

Preparations which have a powerful influence on calcium metabolism may be made from the parathyroids of the ox. If or subcutaneously, the animals deprived of their maintained at a normal far beyond this, either animals and unless the ensue The preparations activity in raising the calcium concentration in parathyroidectomized animals or in normal animals. On subcutaneous and intramuscular injections the plasma calcium begins to rise in about 4 hours, reaches its maximum in from 12 to 18 hours and returns to the previous level in from 20 to 24 hours. Associated with the rise in serum calcium is an increased urinary excretion of calcium and inorganic phosphate. latter. An immunity repeated administrati arations has been shown to be of value in tetania parathyreopriva. In infantile tetany their employment should be confined to those

BETA-HYPOPHAMINE.—Pitressin (PARKE, DAVIS) —

An aqueous solution containing the pressor and diuretic antidiuretic principle of the posterior lobe of the pituitary gland,

is about twice the pressor potency of Posterior Pituitary Injection U S P

Actions and Uses—Beta hypophamine is used for raising the blood pressure, for increasing the muscular activity of the bladder and intestinal tract also for antidiuretic effect in diabetes insipidus (See article Pituitary)

Experimental evidence has been obtained indicating that the product increases the blood sugar and it has been successfully employed to counteract overdoses of insulin in animals. No clinical studies to determine the value for this purpose have been reported so far. It has been suggested that the product may be of value either in conjunction with or supplementary to the use of epinephrine in the treatment of serum sickness and similar vasomotor disturbances, but no definite evidence on this point is as yet available.

Dosage—From 0.3 to 1 cc. intramuscularly, repeated as may be indicated.

PARKE, DAVIS & COMPANY

Solution Pitressin 0.5 cc. and 1 cc. ampuls

U S patent, 1,960,493 (May 29, 1934 expires 1951) U S trademark 254,507

BETA-HYPOPHAMINE TANNATE—Pitressin Tannate (PARKE, DAVIS)—A suspension in vegetable oil of a water insoluble tannate of the pressor and diuretic antidiuretic principle of the posterior lobe of the pituitary gland (beta hy-

{Nov } 1916)

Actions and Uses—Beta hypophamine tannate is recommended for use where the prolonged action of beta hypophamine is desired, particularly for the treatment of patients suffering from diabetes insipidus.

Dosage—From 0.3 to 1 cc. (3 to 5 pressor units) intramuscularly, *not* intrataneously, at intervals of from 36 to 48 hours.

BETA-HYPOPHAMINE.—Pitressin (PARK, DAVIS).—An aqueous solution containing the pressor and diuretic-anti-

ton and Rowe (*J. Lab. & Clin. Med.* 2: 120 [Nov.] 1916) so that each cubic centimeter contains 20 pressor units (1 unit represents the pressor activity exhibited by 0.5 mg. of Posterior Pituitary U. S. P. Reference Standard-U. S. P.) It has, therefore, twice the pressor potency of Posterior Pituitary Injection U. S. P.

Actions and Uses.—Beta-hypophamine is used for raising the blood pressure, for increasing the muscular activity of the bladder and intestinal tract, also for antidiuretic effect in diabetes insipidus. (See article, Pituitary.)

Experimental evidence has been obtained indicating that the product increases the blood sugar and it has been successfully employed to counteract overdoses of insulin in animals. No clinical studies to determine the value for this purpose have been reported so far. It has been suggested that the product may be of value either in conjunction with or supplementary to the use of epinephrine in the treatment of serum sickness and similar vasomotor disturbances, but no definite evidence on this point is as yet available.

Dosage.—From 0.5 to 1 cc. intramuscularly, repeated as may be indicated.

PARK, DAVIS & COMPANY

Solution Pitressin: 0.5 cc. and 1 cc. ampuls.

U. S. patent, 1,960,491 (May 29, 1934, expires 1951) U. S. trademark 254,507.

BETA-HYPOPHAMINE TANNATE.—Pitressin Tannate (PARK, DAVIS).—A suspension in vegetable oil of a water insoluble tannate of the pressor and diuretic-antidiuretic principle of the posterior lobe of the pituitary gland (beta-hypophamine) standardized to contain five pressor units in each cc. (one unit representing the pressor activity exhibited by 0.5 mg. of standard powdered pituitary U. S. P.) It is standardized by the method of Hamilton and Rowe (*J. Lab. & Clin. Med.* 2: 120 [Nov.] 1916).

Actions and Uses.—Beta-hypophamine tannate is recommended for use where the prolonged action of beta-hypophamine is desired, particularly for the treatment of patients suffering from diabetes insipidus.

Dosage.—From 0.5 to 1 cc. (3 to 5 pressor units) intramuscularly, never intravenously, at intervals of from 36 to 48 hours.

BETA-HYPOPHAMINE—Pitressin (PARKE, DAVIS).—

An aqueous solution containing the pressor and diuretic antidiuretic principle of the posterior lobe of the pituitary gland, (betahypophamine) containing less than 1 unit of oxytocic activity per cubic centimeter. Five tenths per cent of chlorbutanol is used as a preservative. It is standardized by the method of Hamilton and Rowe (*J Lab & Clin Med* 2 120 {Nov} 1916) so that each cubic centimeter contains 20 pressor units (1 unit represents the pressor activity exhibited by 0.5 mg. of Posterior Pituitary U S P Reference Standard U S P). It has, therefore, twice the pressor potency of Posterior Pituitary Injection U S P.

Actions and Uses.—Beta hypophamine is used for raising the blood pressure, for increasing the muscular activity of the bladder and intestinal tract, also for antidiuretic effect in diabetes insipidus. (See article Pituitary.)

Experimental evidence has been obtained indicating that the product increases the blood sugar and it has been successfully employed to counteract overdoses of insulin in animals. No clinical studies to determine the value for the treatment of human beings have been conducted. It has been used in the treatment of shock, heart failure, and similar vaso-motor disturbances, but no definite evidence on this point is as yet available.

Dosage.—From 0.3 to 1 cc. intramuscularly, repeated as may be indicated.

PARKE, DAVIS & COMPANY

Solution Pitressin 0.5 cc. and 1 cc. ampuls

U S patent, 1960493 (May 23, 1934 expires 1951) U S trade mark 254,307

BETA-HYPOPHAMINE TANNATE—Pitressin Tannate (PARKE, DAVIS).—A suspension in vegetable oil of a water insoluble tannate of the pressor and diuretic antidiuretic principle of the posterior lobe of the pituitary gland (beta hypophamine) standardized to contain five pressor units per cubic centimeter (one cubic centimeter contains 5 units).

of standardization is the same as that of the Pitressin solution. (See article Pituitary.)

Actions and Uses.—Beta hypophamine tannate is used for raising the blood pressure, for increasing the muscular activity of the bladder and intestinal tract, also for antidiuretic effect in diabetes insipidus.

Dosage.—From 0.3 to 1 cc. (3 to 5 pressor units) intramuscularly, *not* intrathecally, at intervals of from 36 to 48 hours.

ration of the ovarian follicle, which in turn bring on the changes characteristic of estrus; (3) a factor which causes luteinization of the ovarian follicles; (4) a factor which is necessary for normal thyroid development and function and which, if present in excess, produces hyperplasia of the thyroid with hyperthyroidism in both the rat and the guinea pig. (5) a factor which produces lactation in mammals, and possibly plays a part in mammary gland proliferation; it also induces a secretion of crop milk in pigeons; (6) a diabetogenic principle which decreases the hypoglycemic response to insulin and which has been shown experimentally to damage indirectly the cells of the islets of Langerhans thus producing the diabetic syndrome; and (7) a ketogenic principle, apparently distinct from the diabetogenic factor, which increases the ketone content of the blood in

ciples; among these is one which stimulates the adrenal cortex known as the adrenotropic hormone. This has recently been prepared in relatively pure form

The Council believes that extensive clinical trial has failed to establish the value of desiccated pituitary preparations for oral administration whether these are prepared from the anterior or from the posterior lobe

ALPHA-HYPOPHAMINE.—**Pitocin** (PARKE, DAVIS).—An aqueous solution containing the oxytocic principle of the posterior lobe of the pituitary gland (alphahypophamine) containing less than $\frac{1}{2}$ unit of pressor activity per cubic centimeter. Five-tenths per cent of chlorobutanol is used as a preservative. It is standardized by the U. S. P. method for posterior pituitary, each cubic centimeter containing 10 units. *Alpha*-hypophamine therefore has an activity on the uterus equal to that of the U. S. P. solution of pituitary.

Actions and Uses.—*Alpha*-hypophamine is used to stimulate uterine contractions in obstetrical practice and to stop post-operative bleeding.

The use of the product may be particularly indicated in those cases in which increase of blood pressure is undesirable. Its use is contraindicated in contracted pelvis and in incomplete dilatation of the cervix. (See general article, Pituitary.)

PARKE, DAVIS & COMPANY

Solution Pitocin: 0.5 cc. and 1 cc. ampuls.

U. S. patent 1,960,493 (May 29, 1934; expires 1951). U. S. trademark 254,956.

BETA-HYPOPHAMINE—Pitressin (PARKE, DAVIS)—

An aqueous solution containing the pressor and diuretic anti-diuretic principle of the posterior lobe of the pituitary gland, (betahy

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Actions and Uses—Beta hypophamine is used for raising the blood pressure, for increasing the muscular activity of the bladder and intestinal tract, also for antidiuretic effect in diabetes insipidus (See article, Pituitary)

Experimental evidence has been obtained indicating that the product increases the blood sugar and it has been successfully employed to counteract overdoses of insulin in animals. No clinical studies to determine the value for this purpose have

is as yet available

Dosage—From 0.3 to 1 cc intramuscularly, repeated as may be indicated

PARKE, DAVIS & COMPANY

Solution Pitressin 0.5 cc and 1 cc ampuls

U S patent 1,960,493 (May 29, 1934, expires 1951) U S trademark 254,507

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hypophamine) standardized to contain five pressor units in each cc. (one unit representing the pressor activity exhibited by 0.5 mg of standard powdered pituitary U S P) It is standardized by the method of Hamilton and Rowe (*J Lab & Clin Med* 2:120 [Nov.] 1916)

Actions and Uses—Beta hypophamine tannate is recommended for use where the prolonged action of beta hypophamine is desired, particularly for the treatment of patients suffering from diabetes insipidus

Dosage—From 0.3 to 1 cc (3 to 5 pressor units) intramuscularly, never intravenously, at intervals of from 36 to 48 hours

PARKE, DAVIS & COMPANY

Solution Pitressin Tannate in Oil: 5 pressor units in peanut oil, 1 cc. ampuls. Each cc. contains *beta*-hypophamine tannate.

U. S. patent 1,960,493 (May 29, 1934; expires 1951). U. S. trademark 254,507.

POSTERIOR PITUITARY INJECTION-U. S. P.—

Pituitrin (PARKE, DAVIS).—Posterior Pituitary Solution.—"A sterile solution in water for injection of the water-soluble principle or principles from the fresh posterior lobe of the pituitary body of healthy domesticated animals used for food by man. The pituitary body must have been removed from the animal immediately after slaughtering, and then dried or extracted at once or kept frozen until extracted. *The potency of Posterior Pituitary Injection shall be such that 0.1 cc. of the Injection shall possess an activity equivalent to one U. S. P. Posterior Pituitary Unit.*" U. S. P.

For description and standards see the U. S. Pharmacopeia under Posterior Pituitary Injection.

Actions and Uses.—See general article, Pituitary.

Dosage.—For use in obstetrical cases, from 0.2 to 1 cc.; in surgical cases, from 1 to 2 cc., preferably by deep intramuscular injection or subcutaneously.

ABBOTT LABORATORIES

Solution Posterior Pituitary: 0.5 cc. and 1 cc. ampuls

THE ARMOUR LABORATORIES

Solution Posterior Pituitary: 0.5 cc. and 10 cc. ampuls. Preserved with chlorobutanol 0.5 per cent.

ENDO PRODUCTS, INC.

Solution Posterior Pituitary: 0.5 cc. and 1 cc. ampuls. Preserved with chlorobutanol 0.25 per cent.

THE HARROWER LABORATORY, INC.

Solution Posterior Pituitary: 1 cc. ampuls and 10 cc. vials. Preserved with chlorobutanol 0.5 per cent.

LAKESIDE LABORATORIES, INC.

Solution Posterior Pituitary: 1 cc. ampuls and 30 cc. vials. Preserved with chlorobutanol 0.5 per cent.

ELI LILLY AND COMPANY

Solution Posterior Pituitary: 0.5 cc. and 1 cc. ampuls. Preserved with phenol 0.2 per cent

THE WM. S. MERRELL COMPANY

Solution Posterior Pituitary: Preserved with chlorobutanol 0.5 per cent.

PARKE, DAVIS & COMPANY

Solution Pituitrin: 0.5 cc. and 1 cc. ampuls. Preserved with chlorobutanol 0.5 per cent

U. S. trademark 76,722.

E. R. SQUIBB & SONS

Solution Posterior Pituitary: 1 cc. ampuls Preserved with phenol 0.4 per cent

THE UPJOHN COMPANY

Solution Posterior Pituitary: 0.5 cc., 20 cc. vials and 1 cc. ampuls Preserved with chlorobutanol 0.4 per cent

U. S. STANDARD PRODUCTS CO

Solution Posterior Pituitary: 0.5 cc. and 1 cc. ampuls and 10 cc. and 30 cc. vials Preserved with chlorobutanol 0.4 per cent.

WARREN-TEED PRODUCTS COMPANY

Solution Posterior Pituitary: 10 cc. rubber capped vials Preserved with chlorobutanol 0.5 per cent

THE WILSON LABORATORIES

Solution Posterior Pituitary: 0.5 cc. and 1 cc. ampuls Preserved with chlorobutanol 0.5 per cent

PLACENTA

Gonadotropic Substances

Three types of biological substance which stimulate the

The serum of the pregnant mare contains a gonadotropic substance, which acts in a manner very similar to the preparations made from the anterior lobe. This substance is susceptible of refinement to a point where very little inert protein

The urine of pregnant women contains a gonadotropic substance which is distinct from that in the serum of the pregnant

mare in several respects. The latter substance does not pass out into the mare's urine in appreciable amounts, whereas the urine of pregnant women contains abundant amounts of the hormone, which is termed *chorionic gonadotropic substance*.

In rodents injection of pregnancy urine, or certain extracts thereof, induces follicular growth and corpus luteum formation. When the gonadotropic activity of pregnancy urine was first demonstrated by Zondek, it was considered that the responsible substance was secreted by the anterior pituitary. At the time, the concept was advanced that this gonadotropin consisted of two hormones—prolan A, the follicle stimulating hormone, and prolan B, the luteinizing hormone—on the basis of its effect in the rat, mouse and rabbit. Further experimentation, however, has revealed that this substance is a single entity and not com-
than
the
basis

A significant physiological difference between chorionic gonadotropin and preparations from the anterior pituitary is the inability of the former to stimulate to any appreciable extent the ovary of the monkey or gonadotropin into prim: corpus luteum formatio: have observed definite

women and monkeys treated with this substance. In addition, no clearcut endometrial responses have been observed in primates treated in this manner, which indicates conclusively the inability of this substance to stimulate the growth of normal ovarian structures.

The physiological action of chorionic gonadotropin is not limited to the female, but it exerts a definite effect on the male reproductive organs. It is generally agreed that this substance acts on the interstitial cells of the testes, causing them to elabo-

animal. In some animals there may be some increase in the size of the seminiferous tubules, but there is little if any effect on the germinal epithelium. Spermatogenesis is, however, maintained by chorionic gonadotropin in recently hypophysectomized rats, but it is not restored after atrophy or induced in normal immature rats.

The therapeutic application of chorionic gonadotropin has covered a wide range of conditions. Many of the trials have been on an unsound or improperly conceived basis. Its use in the treatment of ovarian disturbance, for example, has no scientific rationale at the present time, although when it was first introduced for the treatment of these dysfunctions the physiological basis for therapy appeared excellent.

from the urine of pregnant women. It is a glycoprotein containing about 12 per cent of galactose. This preparation is standardized in international units. One international unit equals 0.1 mg of a standardized powder (see Council Report, *J A M A* 113: 2418 [Dec. 30] 1939).

Actions and Uses—Its use is recommended in the treatment of gonorrhoea, when there are no systemic lesions, or in

six to eight weeks if no descent is obtained, since excessive therapy may result in undesirable responses of precocious puberty and possibly other harmful reactions.

The diagnosis of cryptorchidism should not include those cases which have been termed pseudocryptorchids, in which the testes are maintained in the inguinal canal as the result of reflex muscular spasm. It will be found that the testes return to the normal scrotal position on gentle handling and warmth.

Chorionic gonadotropin therapy in other disorders is still considered experimental because of the lack of convincing data. The treatment of hypogonadism in the adult is considered experimental at the present time. Its value in the treatment of uterine bleeding of functional nature is also as yet unproved, although numerous reports on this therapy have appeared in

therapy

Dosage—The usual dose in treating cryptorchidism is from 200 to 500 international units two to three times a week. Long-

Preparation —

assayed biologically on infantile rats and compared in this procedure to the International Standard powder. The product is then diluted with sterile sucrose until its biologic activity is equal to that of the International Standard.

GEORGE A. BREON & Co., Inc.

Chorionic Gonadotropin: 5,000 I. U. and 10,000 I. U., 10 cc. vials. A powdered preparation of chorionic gonadotropin packaged in vials which, when treated with the accompanying 10 cc. of phosphate buffer solution, furnishes solutions having a potency of 500 and 1,000 I. U. per cc., respectively.

COLE CHEMICAL CO.

Chorionic Gonadotropin: 1,000 I. U. and 5,000 I. U., 10 cc. vials. Powdered preparations of chorionic gonadotropin which, when diluted with the accompanying 10 cc. vial of sterile distilled water containing 0.2 per cent *meta*-cresol, provide solutions having a potency of 100 and 500 I. U. per cc., respectively.

ENDO PRODUCTS, INC.

Entromone (Powder): 5,000 I. U. and 10,000 I. U., 10 cc. vials. Powdered preparations of chorionic gonadotropin, which when diluted with 9 cc. of the accompanying isotonic solution of sodium chloride and preserved with phenol 0.4 per cent, provides solutions having a potency of 500 or 1,000 I. U. per cc., respectively.

U. S. patent 1,910,298, U. S. trademark 354,550.

LAKESIDE LABORATORIES, INC.

Chorionic Gonadotropin: Bulk ampuls containing 2,000,000 and 5,000,000 I. U.

Manufactured by license under U. S. patent 1,910,298.

Choriogonin (Powder): Bulk.

Choriogonin: 500 I. U. and 1,000 I. U., 5 cc. vials. A powdered preparation

a potency of 100 or 500 I. U. per cc.

Choriogonin: 1,000 I. U., 5,000 I. U. and 10,000 I. U., 10 cc. vials. Vials containing a powdered preparation of chorionic gonadotropin with urea and sodium phosphate which when diluted with the accompanying 10 cc. of sterile distilled water, containing 0.5 per cent phenol, provide a solution having a potency of 100, 500 or 1,000 I. U. per cc., respectively.

U. S. trademark 419,102.

SHARP & DOHME, INC.

"Lyovac" Chorionic Gonadotropin: 2,500 I. U. 5 cc. vials. A powdered preparation which, when diluted with the accompanying 5 cc. of sterile distilled water containing 0.35 per cent

of phenol, provides a solution having a potency of 500 I U. per cc.

E. R. SQUIBB & SONS

Follutein (*Powder*). Bulk.

Follutein: 1,000 I U, 5,000 I U and 10,000 I U Vials containing a powdered preparation of chorionic gonadotropin which when diluted with the accompanying 10 cc of sterile distilled water containing 0.5 per cent of phenol provides a solution having a potency of 100, 500 and 1,000 I U per cc., respectively

Manufacture licensed under U S patent 1,910,298

WINTHROP-STEARNs, INC.

Korotrin 100 I U., 500 I U., 1,000 I U and 5,000 I U, 100 and 500 I U supplied in 2 cc. ampuls. A powdered preparation of chorionic gonadotropin admixed with sucrose which, when diluted with the accompanying 2 cc of sterile distilled water containing 0.2 per cent of *meta* cresol, provides a solution having a potency of 50 I U or 250 I U per cc. respectively. Marketed in boxes of 5 ampuls with 5 ampuls Korotrin diluent and in boxes of 25 ampuls without diluent. 1,000 I U supplied in 10 cc. vials. A powdered preparation of chorionic gonadotropin admixed with sucrose which, when diluted with the accompanying 10 cc of sterile distilled water containing 0.2 per cent of *meta* cresol, provides a solution having a potency of 100 international units per cubic centimeter. Marketed in packages containing 1 or 10 vials with 1 or 10 bottles Korotrin diluent. 5,000 international units supplied in 10 cc. vials. A powdered preparation of chorionic gonadotropin admixed with sucrose which, when diluted with suitable amounts of the accompanying 50 cc. of sterile distilled water containing 0.2 per cent *meta*-cresol, provides solutions having a potency of 100 or 500 international units per cubic centimeter. Marketed in packages containing 1 vial with 1 bottle of Korotrin diluent.

U S trademark 365,943

TESTES

Testosterone, or testicular hormone, has been isolated from testes and used for glandular therapy. The seminal vesicles, prostate and penis undergo severe atrophy. Libido is diminished and sexual activity is depressed. Injections of testosterone will restore these structures and functions to normal. They undergo regression, however, following cessation

a limited extent by percutaneous administration Methyl testosterone, a synthetic derivative, is much more active than testosterone when given orally. The physiological action is similar. Testosterone is not excreted in the urine, and should not be confused with the u
droandrosterone—wh
malin sexual tissue.

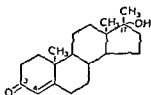
generally marketed in the form of testosterone propionate and methyltestosterone. This substance has shown promise in the replacement therapy of eunuchoidism, but many other claims made by promoters are unwarranted or are still in the experimental stage. The beneficial effects in treating castrates or eunuchoids are present only as long as replacement therapy is continued. The relief of symptoms due to prostatism has been claimed following treatment with this substance but substantial evidence in this regard is lacking. Recent reports indicate that in adequate doses this androgen is effective in treating certain ovarian dysfunctions such as menorrhagia, dysmenorrhea,

considerable (350-400 mg testosterone propionate per month). Recent observations indicate that testosterone may be useful in all
the pain from bone metastasis of mam-
own also to maintain
animal if treatment

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METHYLTESTOSTERONE.—U. S. P.—17-Methyltestosterone. — 17-Methyl- Δ^4 -androstene-17-(α)-ol-3-one. The structural formula of methyltestosterone may be represented as follows:



For description and standards see the U. S. Pharmacopeia under Methyltestosterone and Methyltestosterone Tablets

Dosage.—The dosage and duration of methyltestosterone treatment

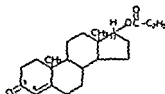
i.e., the third or fourth day after delivery

RARE CHEMICALS, INC.

Tablets Methyltestosterone: 10 mg and 20 mg

TESTOSTERONE PROPIONATE-U. S. P.—The propionic acid ester of testosterone— Δ^4 Androstene 17[α]-propi-

resented as follows



For description and standards see the U. S. Pharmacopeia under Testosterone Propionate

Actions and Uses—Testosterone propionate is primarily useful to supply testicular hormone for the treatment of deficiency or absence of this internal secretion of the male. It may therefore be of value in the treatment of prepuberal and postpuberal eunuchoidism or hypogonadism (deficiency states) and in postcastration or other cause of eunuchism. In the latter instances treatment must be regarded as replacement therapy and is of benefit only as long as it is continued.

Its use in eunuchoidism is intended to promote the develop-

take precedence over the use of androgens

Atrophy of accessory male structures that follows castration

or is associated with eunuchism may also be effectively prevented or these organs restored to normal and maintained by continuous substitution therapy. However, administration of testosterone to normal subjects may induce azoospermia even though no mention of permanent suppression has yet appeared.

The use of testosterone in cryptorchism is subject to certain qualifications: for example, hormonal therapy cannot be effective in this condition, when there is an anatomic lesion causing obstruction of testicular descent. Testosterone propionate is also useful for the treatment of the female in the control of menorrhagia and metrorrhagia and in postpartum inhibition of lactation or breast engorgement.

Dosage.—Testosterone propionate is administered intramuscularly in doses ranging from 5 to 50 mg. from two to six times a week depending on the response obtained. To induce pubescence to 25 mg. three of several weeks. 5 mg. at similar condition and the

effect desired, the maintenance dose must be determined in each individual case. Priapism is indicative of excessive dosage, and its production is an indication for temporary withdrawal of the drug. There has been reported the induction of significant degrees of virilism in women when the amounts of an androgen administered were considerable (350-400 mg. testosterone propionate per month). Testosterone propionate has a standard potency of 50 international capon units per milligram and is usually dissolved in oil for intramuscular injection. For the treatment of menorrhagia, 10 mg. triweekly before the onset of the menses is usually sufficient; in metrorrhagia, 25 mg. on alternate days for a total monthly dosage not to exceed 150 mg. is recommended. For suppression of lactation or breast engorgement, from 25 mg. to 30 mg. every four hours or thrice daily for five or six doses should be administered starting at the beginning of lactation, i.e., the third or fourth day after delivery.

RARE CHEMICALS, INC.

Solution Testosterone Propionate in Oil: 5 mg., 10 mg. and 25 mg. per cc. in sesame oil, 1 cc. ampuls, equivalent to 250, 500 and 1,250 international capon units per cc., respectively, and 25 mg. per cc. in sesame oil, 10 cc. vials.

Solution Testosterone Propionate in Oil with Benzyl Alcohol 3%: 50 mg. per cc., 6 cc. vials.

THYROID

THYROID-U. S. P.—"The cleaned, dried, and powdered thyroid gland previously deprived of connective tissue and fat. It is obtained from domesticated animals that are used for food by man.

"Thyroid contains not less than 0.17 per cent and not more

Agents Used in Metabolic Disorders

In this chapter will be found descriptions of two groups of substances used in the treatment of metabolic disorders: (1) substances that have a special influence on metabolism, like the effect of thiouracil and derivatives on the activity of the thyroid gland; (2) substances that are administered in order that they may be themselves metabolized. The latter include dextrose, amino acids, salts of calcium, certain compounds of iodine and lipotropic agents.

Compounds of iodine for systemic use are described in the chapter on *Thyroid Agents*; those employed for other diagnostic or therapeutic purposes are described in the chapter on *Diagnostic Aids*, as metabolic agents, the chapter on *Hor-*

PROTEIN AND AMINO ACID PREPARATIONS

Protein and amino acid preparations may be conveniently divided into two general classes: (1) mixtures of those amino acids considered essential to human nutrition that are used to combat protein deficiency imposed by severe illness or starvation; (2) individual amino acids that may be used for specific therapeutic purposes.

Preparations in the first class include (a) hydrolysates of protein or sources of protein prepared by various methods of digestion designed to provide adequate amounts of the amino acids, (b) individual amino acids, (c) mixtures of amino acids for parenteral treatment in the treatment of liver disease, (d) amino acids tried in the treatment of liver disease, though

neither are currently recognized to be of specific value in these conditions. Neither methionine nor lysine, although promising for the treatment of liver disease, have been definitely established to be of specific therapeutic value for that condition.

While mixtures of the essential amino acids are presently rec-

ognized to exert a favorable antacid and nutritive effect in peptic ulcer, their primary purpose is to supply dietary nitrogen in readily assimilated form when there is serious interference with the intake, digestion or absorption of dietary protein. There is no evidence that the addition of amino acids to foods will accomplish anything that cannot be accomplished by proper use of proteins as they occur naturally in the diet when there is no such interference.

The amino acids that are now regarded as indispensable for protein synthesis in adult man comprise those which the body is itself unable to synthesize and are generally listed as follows: phenylalanine, tryptophane, methionine, lysine, leucine, isoleucine, threonine, valine, histidine and arginine. These ten amino acids or their precursors are usually provided in mixtures intended for protein replacement in human beings but there is some doubt at present about the indispensability of histidine and arginine in adult man.

As yet there is insufficient information on which to set up exact dosage estimates for the amino acids that are prescribed to meet protein needs of the body. The daily requirements for the individual amino acids are under investigation and there are indications that these range from 0.3 to 5 Gm. each per day. Until more is known of human requirements, amino acid preparations must be given in sufficient quantities to provide every essential constituent in substantial amounts. This may be based on the commonly recommended optimum daily intake of total dietary protein: 1 Gm./Kg. of body weight or about 70 Gm. daily for the average adult man. This figure is based on the fact that on a mixed diet the average protein intake necessary to maintain nitrogen balance has been found to be about 45 grams. There are wide variations in individual requirements and also wide variations in the biologic value of proteins from different sources but it is estimated that the amino acid requirements will ordinarily be met on a diet containing 70 Gm. of protein.

Amino acid mixtures have appeared on the market in various forms: protein hydrolysates or hydrolytic products of good sources of protein in solution or powdered form for oral administration or intravenous injection; mixtures of amino acids in tablet form; synthetic amino acids in tablet form; synthetic amino acids combined with vitamins in tablets and elixirs; protein meals for use in tablets or food fortification. Most tablets or elixirs supply insignificant amounts for rational use in human nutrition.

Thus far the Council considers as acceptable for nutritional purposes only those mixtures that provide adequate amounts of each of the essential amino acids. For the present and until more evidence becomes available the Council restricts acceptance of such amino acid mixtures for either oral or intravenous administration to hydrolysates of suitable pure proteins (such as casein) or good sources of protein (such as blood) in which more than 50 per cent of the total nitrogen present is in the form of alpha amino nitrogen. This minimum degree of hy-

hydrolysis is considered essential to justify the designation of such products as hydrolysates and to reduce the non-antigenic properties of the mixtures used for intravenous injection and those used orally for infants and children who may be allergic to protein of the diet. The Council requires that evidence of non-antigenicity for each product should be submitted. The Council has permitted the addition of carbohydrate to such hydrolysates in proportions suitable for injection. The Council has not, as yet, accepted preparations containing added vitamins or other substances considered essential for adequate nutrition pending adequate justification for such preparations.

Hydrolysates of pure proteins such as casein, lactalbumin and fibrin are properly described as "protein hydrolysates" and are defined under this general heading in the monograph below. They may be designated as "Casein (Lactalbumin, Fibrin) Hydrolysate." Hydrolysates of good sources of protein such as blood, liver and yeast are distinguished from pure protein hydrolysates and will be individually described under separate generic designations appropriate to indicate their respective derivation: "Blood (Liver, Yeast) Hydrolysate. Restored."

amino acids to hydrolysates. "essential" for human nutrition. the equivalent of the bioactive amount proportionate to the original, or sufficient to meet actual requirements if the quantity needed is known. Products to which one or more amino acids have been restored or added or in which one or more of them have been at least partially removed should be designated as "Modified Casein (Liver, etc.) Hydrolysate." When carbohydrate such as dextrose has been added, the designation of such preparations should be expanded to indicate the carbohydrate component, e.g., "(Modified) Casein Hydrolysate with Dextrose () per cent." When such products are supplied in the form of solution for intravenous injection, the designation should be prefixed by the word "Solution" and include the per cent of hydrolysate provided, e.g., "Solution Casein Hydrolysate 5 per cent (with Dextrose 5 per cent)." Such designations do not preclude, but should be adequately displayed with, acceptable trademark names. The Council requires that all hydrolysates be labeled with the appropriate generic designation (to include dextrose or other suitable carbohydrate when this is added), the identity of the protein or source of protein from which they are derived when this is not declared in the descriptive designation, the method of hydrolysis (acid, enzymatic or other), the nature of modification in amino acid content after hydrolysis (if any), the per cent of each amino acid or its equivalent that is present, and the percentage of alpha amino nitrogen that is represented in relation to the total nitrogen content of the mixture. Council consideration of hydrolysates for acceptance is further predicated on adequate rat growth studies to demonstrate nutritive value and in the case of intravenous products, also on adequate clinical evidence to demonstrate freedom from antigenic, pyrogenic and toxic properties. Claims

for special therapeutic purposes of hydrolysates other than for general protein deficiencies must be supported by specific scientific evidence

Pure synthetic mixtures of amino acids for nutritional states or preparations of the individual pure amino acids used for specific therapeutic purposes will be given consideration as evidence for their usefulness is established. Preparations of intact proteins used orally as food supplements are considered to be outside the purview of the Council unless specific therapeutic value is established for such products.

Mixtures Containing Amino Acids

AMINOPEPTODRATE—**Caminoids** (ARLINGTON)—An enzymatic digest of extracted liver and beef muscle wheat gluten, soya yeast casein and lactalbumin with dextrose maltose and sucrose containing amino acids and polypeptides equivalent to proteins (N x 6.25) 45% and carbohydrates 40% to provide a total of 350 available calories per 100 Gm

Actions and Uses—Aminopectodrate is used to supplement the diet in conditions in which specially high protein intake is indicated and it is not feasible to accomplish this by use of ordinary foods See monograph on Protein Hydrolysates

Dosage—Aminopectodrate provides the average adult daily protein requirement when administered in amounts of one Gm per kg of body weight per twenty four hour period It is administered orally in either hot or cold liquids as suited to the patient

ARLINGTON CHEMICAL COMPANY

Caminoids 1701 Gm 4536 Gm 2.27 kg and 4.54 kg containers One tablespoonful (9 Gm) contains 4 Gm of protein as partial hydrolysate

PROTEIN HYDROLYSATES—**Amigen** (MEAD JOHNSON)—**Elamine** (INTERCHEMICAL)—**Paranamine** (WINTHROP STEARNS)—**Protolysate** (MEAD JOHNSON)—These are broadly defined as artificial digests of protein derived by acid enzymatic or other hydrolysis of casein lactalbumin fibrin or other suitable proteins that supply the approximate nutritive equivalent of the source protein in the form of its constituent amino acids They are required to have more than half of the total nitrogen present in the form of alpha amino nitrogen Such preparations comprise (a) unmodified products in which there is neither partial removal nor restoration of any of the original amino acid precursors and for which the designation "protein (or casein etc) hydrolysate" is restricted and (b) modified products to which one or more amino acids have been added or one or more of them have been at least partially removed after hydrolysis and for which the designation "modified protein (or casein etc) hydrolysate" is required. Other labeling require

ments and the permissible modifications in amino acid composition or the addition of carbohydrate are set forth in the foregoing general statement on Proteins and Amino Acid Preparations.

Actions and Uses.—Parenteral preparations are useful for the maintenance of positive nitrogen balance in conditions where there is interference with ingestion, digestion or absorption of food. These conditions are most frequently encountered in illness and after surgery. In the acute conditions, the use of these preparations in persons who be- come unable to take food is of great value. It is difficult to achieve adequate nutrition in these conditions, and the use of these preparations which can be administered intravenously or intramuscularly, is of great value in illness has not been fully appreciated.

Whether hydrolysates should be employed under these circumstances Protein hydrolysates should not be employed as a substitute for food proteins if the latter can be adequately utilized. Intravenous injection is contraindicated in acidosis until the latter condition is corrected. Injection may produce untoward effects such as nausea, vomiting, hyperpyrexia, vasodilatation, abdominal pain, convulsions, edema at the site of injection, phlebitis and thrombosis. Care must be exercised in looking for reactions that indicate danger. Many unfavorable reactions have been traced to inadequate care in the cleanliness of equipment, and also to too rapid administration. Solutions that are cloudy, that contain sediment or have been opened for a previous injection should not be used. Unopened solutions should be stored in a cool place.

Claims for oral use of protein hydrolysates that are shown to be adequate nutritionally should, for the present, be limited as follows:

(1) In the diet of infants allergic to milk when the allergy cannot be met by other foods.

(2) In the treatment of peptic ulcer and in ulcerative colitis if acceptable evidence is submitted pertaining to the product concerned.

It is also suggested that in cases in which a specially adapted diet is required, the use of these preparations may be of value to accomplish the desired results.

Claims for supplementing the protein in other conditions are not permissible because there is no evidence of need for such supplementation and if it should exist it can be met by the use of ordinary foods.

Dosage—See foregoing general statement on Protein and Amino Acid Preparations. Until more is known of the individual requirements of patients, the following dosage is suggested: 10 to 20 cc. of the 10 per cent solution, 3 or 4 times a day.

INTERCHEMICAL CORPORATION, BIOCHEMICAL DIVISION

Elamine Lyophilized: 850 cc. bottle containing 60 Gm. of a dry modified casein hydrolysate (to be diluted to a 10 per cent solution).

cent solution) prepared by acid digestion and consisting essentially of amino acids from which glutamic and aspartic acids have been partially removed and to which DL tryptophane has been added

Solution Elamine (modified casein hydrolysate) 10% with Dextrose 5% 600 cc bottles An acid hydrolysate of casein from which glutamic and aspartic acids have been partially removed and to which tryptophane has been added It is virtually salt free No preservative is added

U S patent pending

MEAD JOHNSON & COMPANY

Amigen (Powder) 454 Gm. containers

Solution Amigen 3½% with Dextrose 3½% in ½ Lactate Ringer's Solution 500 cc bottles Each 100 cc. contains 3½ Gm of Amigen and 3½ Gm of dextrose in ½ the usual concentration of lactate-Ringer's solution

Solution Amigen 5% with Dextrose 5% Bottles of 125 cc 500 cc. and 1 000 cc. Each 100 cc contains 5 Gm of Amigen and 5 Gm of dextrose

Solution Amigen 10% 125 cc. and 500 cc. bottles Each 100 cc. contains 10 Gm of Amigen

U S trademarks 331 523 387 310 427 992

Protolysate (Powder) 454 Gm containers A casein hydrolysate prepared by digestion with fish caeca for oral administration

U S trademarks 425 263 and 423,772

WINTHROP STEARNS INC.

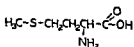
Solution Parenamine 15% Bottles of 100 cc. contain 15 Gm. of casein hydrolysate, consisting essentially of amino acids per 100 cc. of solution.

WYETH INC.

Lactamin (Powder) 0.45 kg cans. A pancreatic digest of lactalbumin containing amino acids and polypeptides equivalent to 92 per cent hydrolyzed protein providing 90 calories per 28.35 Gm It has 50 per cent of its total nitrogen as amino nitrogen and contains no fats or carbohydrates To be administered orally

Individual Amino Acids

METHIONINE—Meonine (WYETH)—DL-Methionine—γ-Methylthiol α aminobutyric acid—The structural formula for DL Methionine may be represented as follows



For tests and standards, see Section B.

Actions and Uses.—Methionine is a sulfur containing amino

hepatic lesions

Severe liver damage is regularly caused in protein depleted dogs by chloroform anesthesia and this is altogether prevented by methionine. Lean beef and other high protein diets are equally effective. A similar protective effect has been demonstrated against other hepatotoxic agents such as oxophenarsine in animal experiments.

The striking results of these animal experiments have led to the use of methionine in the treatment of liver disease in man, especially in acute toxic hepatitis and toxic hepatitis due to carbon tetrachloride. In the treatment of these conditions, methionine has been used in various methods of treatment. The improvement in the condition of the liver is due to the methionine alone.

There is no doubt that methionine is a superior foodstuff.

Methionine in large amounts. But because of its great theoretical interest and in the hope that some special utility may be found, methionine has been accepted for experimental purposes only.

Of low toxicity, the use of methionine is not likely to be attended by any untoward effects.

Dosage.—As a supplement to a high protein diet, 3 to 6 Gm. daily is usually administered in tablet form. In severe cases 10 to 20 Gm. has been used. When oral administration is not feasible, crystalline methionine may be given in amounts of 5 to 10 Gm. daily by slow intravenous drip as a 3 per cent solution in Dextrose Injection, U. S. P., or Water for Injection, U. S. P., that has been further sterilized by autoclaving.

WYETH INCORPORATED

Crystalline Meonine (Powder): 50 Gm. bottles.

Tablets Meonine: 0.5 Gm

U. S. trademark 406,590

ANTITHYROID DRUGS

PROPYLTHIOURACIL. — 6-propyl-2-thiouracil — The structural formula of propylthiouracil may be represented as follows:



For tests and standards, see Section B

ism

iodine therapy

Not all patients experience a permanent remission following

substitute for operative procedure can be determined only by following the results of investigations carried on for longer periods

In the preparation of patients for operation, propylthiouracil reduces the basal metabolic rate to a more nearly normal level than can be brought about by the use of iodine alone. The extreme vascularity and friability of the gland that has been encountered at operation following the preoperative administration of thiouracil derivatives alone has been overcome by a

therapy commenced immediately on the detection of signs of any of these complications

Since the mild and the juvenile types of hyperthyroidism can frequently be controlled adequately by iodine therapy alone, propylthiouracil should not be used for these patients unless the safer form of therapy proves ineffective.

Dosage.—For severe cases of hyperthyroidism, initial doses of 50 mg. every eight hours appear to be effective in routine treatment, and 50 mg. twice daily in milder cases. Iodine should be administered for two or three weeks immediately before thyroidectomy.

The effective dose of propylthiouracil should be continued until all signs and symptoms of the disease have been brought under control. Adequate maintenance dosage may best be established by determinations of the basal metabolic rate. Patients should be instructed to cease medication and report to their physician immediately if any adverse symptoms such as sore throat, fever, coryza or malaise are experienced

ABBOTT LABORATORIES

Tablets Propylthiouracil: 25 mg. and 50 mg.

LEDERLE LABORATORIES, DIVISION AMERICAN CYANAMID CO.

Tablets Propylthiouracil: 50 mg.

ELI LILLY & CO.

Tablets Propylthiouracil: 50 mg.

THE UPJOHN COMPANY

Tablets Propylthiouracil: 50 mg.

CALCIUM COMPOUNDS

Calcium compounds are used therapeutically for the purpose of overcoming calcium deficiency. The systemic action induced by calcium is dependent on the dosage and the mode of administration, which are in turn dependent upon the calcium salt that is used. Relatively insoluble salts of calcium are restricted to

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...ous injection further
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...the same reason other
...s ammonium chloride
...with the use of less
irritant alkaline calcium salts in the treatment of hypocalcemia

The gluconate and levulinate salts, containing 9 and 13 per cent calcium respectively, are relatively nonirritating for subcutaneous or intramuscular injection. Muscle necrosis, however, has followed such administration in children, so that the injection of calcium compounds into the tissues should be restricted to adults

Calcium salts are specific in the treatment of hypocalcemic tetany. Vitamin D or parathyroid hormone may also be indicated

increase the absorption of calcium when this is deficient

The chloride, lactate or carbonate salts of calcium are all suitable for oral administration in doses corresponding to their percentage of calcium content. Chemical compounds represented by such salts as the citrate, oxylate or phosphate, that are capable of precipitating or combining with ionized calcium of the blood when taken in large amounts, should probably be

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calcium phosphate has been administered orally when phosphorus as well as calcium is deficient, but its use should

It has been reported that a relative deficiency of calcium is associated with insensitivity of the uterus to oxytocics and that calcium potentiates the action of the latter agents. In none of the foregoing conditions, however, is there sufficient clinical evidence for the therapeutic use of calcium and none is ordinarily associated with a demonstrable deficiency. Such uses are mostly empirical and have not been substantially supported by

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the tissues, and the presumed antispasmodic effect on smooth muscle has not been confirmed by experimental observations. The cardiac and uterine effects of calcium are dependent on optimum concentrations, so that the role of calcium in regulating the muscular functions of these structures has little or no clinical application. Hypercalcemia has been reported to increase the toxicity of digitalis, but this is largely theoretical. Intravenously, overdoses may fatally paralyze the heart and the central nervous system; intravenous injection should be made very slowly.

The therapeutic use of calcium in the absence of demonstrable deficiency of that cation in the blood or extracellular fluids is considered irrational. In ordinary dietary deficiency the administration of calcium compounds should not take precedence over a remedial diet well balanced in the choice of foods rich in calcium.

AFENIL (BILHUBER-KNOLL).—This preparation is a molecular compound of calcium chloride and urea.

For tests and standards, see Section B.

Actions and Uses.—This molecular compound has the actions of calcium chloride. It is claimed that its solutions, when administered intravenously, are better tolerated and less irritating than solutions of calcium chloride.

Dosage.—The product is marketed in ampuls containing 10 cc of a 10 per cent solution of the molecular compound. Each injection consists of the entire contents of one ampul.

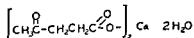
BILHUBER-KNOLL CORP.

Solution Afenil 10%: 10 cc. ampuls containing a solution equivalent to 0.11 Gm Ca.

U. S. trademark 170,032. German patent 306,804

CALCIUM LEVULINATE-N.F.—"A hydrated calcium salt of levulinic acid and contains not less than 97.5 per cent and not more than 100.5 per cent of $(\text{CH}_3\text{CO}(\text{CH}_2)_2\text{COO})_2\text{Ca}$ calculated on a dry basis, the loss on drying being determined on a separate portion by drying at 105 C. for 24 hours."—N. F.

The structural formula may be represented as follows:



For description and standards see The National Formulary under Calcium Levulinate and Calcium Levulinate Ampuls.

Actions and Uses.—Calcium levulinate is used to obtain the therapeutic effects of calcium. It may be administered orally or intravenously and is virtually nonirritant for subcutaneous or intramuscular injection.

Dosage.—By injection, for adults, 1 Gm. daily or on alternate

days, for children, 0.2 to 0.5 Gm Orally, for adults, 4 to 5 Gm three times a day, for children, 1 to 2 Gm three times a day

CHEMO PURO MANUFACTURING CORP

Calcium Levulinate (*Powder*) 30 Gm and 480 Gm bottles.

THE J F HARTZ COMPANY

Solution Calcium Levulinate 10% 1 Gm, 10 cc ampuls

PAUL-LEWIS LABORATORIES INC

Calcium Levulinate (*Powder*) Bulk. Packaged in units of 500 Gm and multiples thereof

CARROLL DUNHAM SMITH PHARMACAL CO

Solution Calcium Levulinate 10% 1 Gm 10 cc ampuls

IODINE COMPOUNDS FOR SYSTEMIC USE

These are typified by sodium iodide and potassium iodide. The mechanism of their action is not clearly understood. The most definite results are seen in the rapid absorption of certain

effective in the prophylaxis of simple endemic goiter, and in controlling the symptom of hyperthyroidism in preparation for operation

Iodine compounds with proteins and fats have been introduced with claims that they are less irritating to the digestive tract and that they are less inclined to set up the disagreeable symptoms of iodism, such as coryza and skin eruptions. Expe-

establish the fact
ly employed are

the tissues, and the presumed antispasmodic effect on smooth muscle has not been confirmed by experimental observations. The cardiac and uterine effects of calcium are dependent on optimum concentrations, so that the role of calcium in regulating the muscular functions of these structures has little or no clinical application. Hyperventilation has been reported to increase the to
Intravenously,
central nervous
very slowly.

The therapeutic use of calcium in the absence of demonstrable deficiency of that cation in the blood or extracellular fluids is considered irrational. In ordinary dietary deficiency the administration of calcium compounds should not take precedence over a remedial diet well balanced in the choice of foods rich in calcium.

AFENIL (BILHUBER-KNOLL).—This preparation is a molecular compound of calcium chloride and urea.

For tests and standards, see Section B.

Actions and Uses.—This molecular compound has the actions of calcium chloride. It is claimed that its solutions, when administered intravenously, are better tolerated and less irritating than solutions of calcium chloride.

Dosage.—The product is marketed in ampuls containing 10 cc. of a 10 per cent solution of the molecular compound. Each injection consists of the entire contents of one ampul.

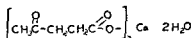
BILHUBER-KNOLL CORP.

Solution Afenil 10%: 10 cc. ampuls containing a solution equivalent to 0.11 Gm Ca.

U. S. trademark 170,032. German patent 306,804.

CALCIUM LEVULINATE-N.F.—"A hydrated calcium salt of levulinic acid and contains not less than 97.5 per cent and not more than 100.5 per cent of $(\text{CH}_3\text{CO}(\text{CH}_2)_2\text{COO})_2\text{Ca}$ calculated on a dry basis, the loss on drying being determined on a separate portion by drying at 105 C. for 24 hours"—N. F.

The structural formula may be represented as follows:



For description and standards see The National Formulary under Calcium Levulinate and Calcium Levulinate Ampuls.

Actions and Uses.—Calcium levulinate is used to obtain the therapeutic effects of calcium. It may be administered orally or intravenously and is virtually nonirritant for subcutaneous or intramuscular injection.

Dosage.—By injection, for adults, 1 Gm daily or on alternate

days, for children 0.2 to 0.5 Gm Orally for adults 4 to 5 Gm three times a day, for children, 1 to 2 Gm three times a day

CHEMO PURO MANUFACTURING CORP

Calcium Levulinate (Powder) 30 Gm and 480 Gm. bottles

THE J F HARTZ COMPANY

Solution Calcium Levulinate 10% 1 Gm 10 cc ampuls

PAUL LEWIS LABORATORIES INC.

Calcium Levulinate (Powder) Bulk. Packaged in units of 500 Gm. and multiples thereof

CARROLL DUNHAM SMITH PHARMACAL CO

Solution Calcium Levulinate 10% 1 Gm 10 cc ampuls

IODINE COMPOUNDS FOR SYSTEMIC USE

These are typified by sodium iodide and potassium iodide. The mechanism of their action is not clearly understood. The

value and has been superseded by more promising agents. The

operation

Iodine compounds with proteins and fats have been introduced with claims that they are less irritating to the digestive tract and that they are less inclined to set up the disagreeable symptoms of iodism such as coryza and skin eruptions. Expe-

mic goiter and in
in preparation for

to produce the full effects such as are required in the treatment of syphilis. It may suffice however in conditions for which a milder action is desired. Clinical observations establish the fact that the organic iodides in the dosage ordinarily employed are weaker than full doses of the inorganic forms

Warning: The use of iodides should be restricted to oral administration. The dangers attending intravenous injection of sodium iodide, i.e., acute and violent iodism, colloidoclastic shock and pulmonary edema, outweigh the doubtful advantages to be gained by this route of administration.

METHENAMINE TETRAIODIDE.—Siomine (PITMAN-MOORE).—Hexamethylenetetramine tetraiodide. — Siomine contains 78.5 per cent of iodine.

For tests and standards, see Section B.

Actions and Uses.—Methenamine tetraiodide is decomposed in the intestine with formation of hexamethylenetetramine and iodine, the rate of absorption and excretion being essentially the same as that of ordinary (inorganic) iodides; before it produces the effects of ordinary (inorganic) iodides, it differs only in that it

is a hexamethylenetetramine component of methenamine tetraiodide, which serves only to render the substance insoluble. While ordinarily the hexamethylenetetramine content of methenamine tetraiodide may be ignored, the drug should be discontinued if any signs of hexamethylenetetramine intolerance arise, such as vesical irritation or hematuria.

Dosage.—Orally, 0.3 Gm. methenamine tetraiodide is best administered in capsule form during or immediately following meals.

PITMAN-MOORE COMPANY, DIVISION OF ALLIED LABORATORIES, INC.

Capsules Siomine: 60 mg., 0.13 Gm. and 0.3 Gm.

U. S. patent 1,226,394 (May 15, 1917; expired). U. S. trademark 107,998.

Iodized Fats and Fatty Acids

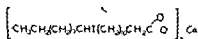
Iodized fats and iodized fatty acids produce, in general, the same systemic effects as ordinary (inorganic) iodides; their iodine, however, is more slowly absorbed and excreted, and therefore more persistently retained, especially in tissues rich in lipoids, such as the nervous structures.

Iodized fats and iodized fatty acids produce in general the same effects as ordinary (inorganic) iodides; but their iodine is more slowly absorbed and excreted, and therefore more persistently retained, especially in tissues rich in lipoids,

The iodized fats and fatty acids generally pass the stomach unchanged, and are saponified and absorbed in the small intestine, like ordinary fats. They are then deposited for the most part in lipoid tissues, where they are gradually oxidized, yielding inorganic iodide which is given off to the blood and excreted. The iodine content of the blood is thus maintained more uniform than when inorganic iodides are administered.

It is conceivable that iodized fats and fatty acids have therapeutic advantages over ordinary iodides when a gradual long sustained iodide action is desired but the clinical evidence is not decisive. The doses used in these conditions as a rule are not irritating to the stomach and are not likely to produce iodism. Hypodermic injections remain unabsorbed for long periods and do not produce systemic actions except in very hypersensitive individuals for instance in tuberculosis.

CALCIUM IODOBEHENATE U S P—Sajodin (WINTHROP STEARNS) —Calcium Monoiodobehenate — Consists principally of calcium moniodobehenate $[(C_{21}H_{41}ICOO)_2Ca]$ and contains when dried at 100 C for two hours not less than 23.5 per cent of I [iodine] —U S P The structural formula may be represented as follows



For description and standards see the U S Pharmacopoeia under Calcium Iodobehenate

Actions and Uses—Calcium iodobehenate is used as a substitute for the inorganic iodides. See general article Iodized Fats and Fatty Acids

Dosage—0.5 Gm.

WINTHROP STEARNS INC.

Sajodin (Powder) Bulk.

Tablets Sajodin 65 mg and 0.52 Gm

U S patent 839 509 (Dec 23 1906 exp red) U S trademark 61 730

IODINATED CASTOR OIL—Riodine (Astier) (GALLIA LABS) —A 66 per cent solution in oil of an iodine addition product of castor oil prepared by treating castor oil with hydrogen iodide. Iodinated castor oil contains about 17 per cent of iodine.

For tests and standards see Section B

Actions and Uses—Iodinated castor oil is used as a substitute for the inorganic iodides. See general article Iodized Fats and Fatty Acids.

Dosage—From 0.4 to 1.2 Gm per day in pearls taken after meals. Supplied only in the form of pearls

GALLIA LABORATORIES INC.

Pearls Riodine 0.2 Gm.

U S trademark 86 974

IODOBASSID—Lipodine (CIBA) —See Iodobrassid under Iodized Oils in the chapter on Diagnosis Aids

Actions and Uses.—Choline dihydrogen citrate has been used in the treatment of hepatic diseases associated with decided fatty infiltration. In the experimental animal it has been demonstrated that a fatty liver can be produced by a diet free of choline and that the fatty administration suffering from conclusive, but the results have been sufficiently promising to warrant trial of the agent the liver in conjunction. However, the results of cirrhosis of the liver have been disappointing.

The normal diet contains large amounts of choline, and there is no valid evidence that a pathologic state due to choline deficiency exists in man. The possibility of such a deficiency seems unlikely because of the amount of choline present in most food stuffs. In addition, it has yet to be conclusively demonstrated that choline therapy is superior to an adequate diet in the treatment of liver disease.

Dosage—Two to 3 Gm. of choline dihydrogen citrate (8 cc. to 12 cc. of the 25 per cent syrup) in divided doses. Choline is always administered orally.

FLINT, EATON & Co.

Syrup Choline Dihydrogen Citrate: 475 cc. bottles. A flavored syrup containing 25 per cent of choline dihydrogen citrate. Each 4 cc. contains 1 Gm of choline dihydrogen citrate.

Oxytocics

Ergot, the dried sclerotium of *Claviceps purpurea* developed on rye, contains a number of specific alkaloids to which it owes its therapeutic effects. In addition, a great variety of chemical

optical isomers one member of each pair being pharmacologically potent and the other member almost inert. The members of each pair may be interconverted by chemical procedures, and it has been suggested that the inert alkaloids may be formed to some extent from the active ones in the process of extraction.

The isomeric pairs of alkaloids may be listed as follows:

Potent	Relatively Inactive	Formula
1 Ergotoxine	Ergotamine ψ Ergotamine	$C_{25}H_{35}O_8N_3$
2 Ergotamine	Ergotamine	$C_{25}H_{35}O_8N_3$
3 Ergosine	Ergosine	$C_{20}H_{27}O_5N_2$
4 Ergocristine	Ergocristine	$C_{20}H_{27}O_5N_2$
5 Ergonovine	Ergometrine	$C_{20}H_{27}O_5N_2$

It may be noted that the first of the five groups consists of three rather than of two members and furthermore that the

with each other
of ergonovine is
The inert alka-

oids in solution in chloroform show a high degree of dextro-

to account for differences in methods of the same pair. The various pairs of alkaloids differ in the other products of hydro-

ysis, which are unique in the field of alkaloidal chemistry in that certain of them are amino acids. These groups undoubtedly determine the variations in pharmacologic action shown by the active alkaloids of different pairs, e. g., ergotoxine and ergonovine.

Ergotoxine may be crystallized from benzene, carbon bisulfide and acetone. It is insoluble in water and light petroleum, sparingly soluble in ether, and very soluble in methyl and ethyl alcohol, chloroform, acetone and ethyl acetate. The phosphate of ergotoxine is soluble in 313 parts of water at room temperature; the ethanesulfonate is sparingly soluble in water, somewhat more soluble in ethyl alcohol, and dissolves readily in methyl alcohol. Ergotinine is insoluble in water, sparingly soluble in ethyl alcohol, and very readily soluble in chloroform.

Ergotamine crystallizes from aqueous acetone, methyl alcohol, ethyl alcohol and benzene. It is insoluble in water and less soluble than ergotoxine in benzene, chloroform and ether, but is readily soluble in nitrobenzene, pyridine and dilute sodium hydroxide. It forms a tartrate, a methanesulfonate, and a phosphate, all of which are water soluble. Ergotaminine is fairly soluble in chloroform and in nitrobenzene, and readily soluble in pyridine. It is much less soluble than ergotamine in other solvents from which it crystallizes relatively solvent-free, unlike most of the ergot alkaloids which tend to retain solvent of crystallization.

Ergonovine may be crystallized from a number of solvents,

of the mine, tent o differe same locality. It occurs in lower concentrations (up to 0.4 mg. per Gm. of ergot) than does the ergotoxine-ergotamine group, which may reach 2 mg. per more basic than ergonovine only slightly soluble in wa acetone. It forms crystalline the inert series.

ergotamine, ergosine, and pre the same type of pharma- idual variations have been observed.

They cause a moderate and prolonged increase in tone and rhythmic smooth m by arteriol pressure may be seen.

effector responses of the sympathetic nervous system. In sufficient dosage cyanosis of the cockscomb and with toxic doses gangrene through peripheral vasomotor paralysis develop.

demonstrated on other smooth muscle organs, more readily on those to which the sympathetic nerve supply is predominantly motor, such as the rabbit uterus. Poisonous doses in the intact animal produce acute manifestations essentially due to central stimulation consisting of excitement, tremor, weakness, pyrexia,

ergotoxine.

Ergonovine is effective on the uterus in smaller doses and concentrations than are the other alkaloids. This difference is particularly apparent in the puerperal state when the uterus is

on the central nervous system and peripheral vascular mechanism vary with the animal and with experimental conditions. A slight increase in blood pressure may be encountered clinically. Ergonovine shows a definite sympathomimetic effect and little or no inhibition of epinephrine action. Although it produces the characteristic cockscomb reaction, it shows definitely less tendency to produce gangrene than ergotoxine and ergotamine. It is less toxic than these two alkaloids, but in poisonous doses produces similar effects.

Assay—All ergot preparations, especially those containing water, deteriorate with age. It is necessary therefore to standardize them, and the date of assay should be indicated on the container.

Ergot is assayed officially in this country by the cockscomb method (see U. S. P. XIX) which may vary at a rate of

lysergic acid component, has been extensively used. Such methods do not distinguish between ergonovine and the ergotoxine-ergotamine group, and consequently are not a true measure of the pharmacologic potency unless a constant proportion of these groups in various ergots could be assumed. To overcome this difficulty, assays involving a previous separation of the two groups have been suggested.

particular action.

ERGOT ASEPTIC.—A liquid extract of ergot, standardized by the cockscomb method of assay to have the same potency as fluidextract of ergot. U. S. P.

on the human uterus when ergot is used clinically.

Ergot causes powerful tonic, sometimes tetanic, contractions

final cause of the vascular occlusion from ergotism.

The principal use of ergot is to prevent postpartum hemorrhage. For this purpose a full dose is sometimes given as soon as the second stage of labor terminates, but it should not be given until the placenta has been expelled. Its use during labor should be avoided, as it may cause rupture of the uterus or asphyxia of the child. It is employed as a prophylactic for "after-pains." Ergot is also used for hemorrhage from the uterus in menorrhagia and metrorrhagia. Its use for hemorrhage from other internal organs is not rational.

Dosage.—1 to 2 cc. Ergot aseptic is intended for intramuscular injection. Ergot aseptic is marketed in ampuls only. The date of manufacture appears on each package and the product is not guaranteed to possess its full potency for more than one year from time of manufacture.

Preparation—

Ergot is extracted with diluted alcohol acidulated with hydrochloric acid. The percolate is partially neutralized with alkali and concentrated by distillation in a partial vacuum at a temperature not above 80 C. A large excess of alcohol is added to the concentrated percolate and the material which precipitates is removed. The liquid portion is freed from alcohol

potency.

Ergot aseptic is standardized to the same potency as fluidextract of ergot-U. S. P., as determined by the cockscomb method described in the U. S. P. XII.

PARKE, DAVIS & COMPANY

Ampule Ergot Aseptic: 1 cc

ERGOTAMINE TARTRATE-U. S. P.—Gynergen (SANDOZ).—"The tartrate of an alkaloid obtained from ergot." U. S. P.

For description and standards see the U. S. Pharmacopeia under Ergotamine Tartrate and Ergotamine Tartrate Tablets

Actions and Uses—Ergotamine tartrate stimulates smooth muscle thus causing an increase in blood pressure, contraction of the uterus, etc. (the isolated uterus of the guinea pig is affected in dilutions of from 1 in 150,000,000 to 1 in 200,000,000). In large doses it paralyzes the cellular response to the effector fibers of the sympathetic nervous system. It causes the darkening of the coxcomb characteristic of the action of ergot and in toxic doses causes gangrene and convulsions. There is evidence that ergotamine tartrate relieves the pain and shortens the attack in many cases of migraine. However, before relief occurs, nausea and vomiting may be increased. The drug should not be used as a prophylactic. Caution in its use is advisable on account of the danger of poisoning from long continued use or overdosage.

Ergotamine tartrate may be used when the action of ergot to produce uterine contraction is desired, it is contraindicated whenever tonic contraction of the uterus would be dangerous. Ergotamine tartrate is also stated to be indicated in hemorrhage following abortion, after curettage and in postpartum endometritis.

Dosage—Intramuscularly, the average dose is 0.25 mg., orally, 1 mg. two to four times daily. Caution should be exercised in the repeated use of ergotamine, cases of gangrene have been reported where the use of the alkaloid has been continued over a period of some days. For more on the dosage see U. S. P.

when the drug is given by the subcutaneous route.

SANDOZ CHEMICAL WORKS, INC.

con-
tar-
ig of

Tablets Gynergen: 1 mg

U. S. patent 1,394,233 (Oct. 18, 1921, expired); 1,435,187 (Nov. 14, 1922, expired) U. S. trademark 173,047

Parenteral Solutions

This chapter includes preparations for injection that are used to supply water, salts or ions to replace lost body fluid, combat dehydration, restore electrolyte balance, and replenish the buffer system of the blood.

Solutions of dextrose, sometimes used to combat water loss or to encourage output of fluid, and solutions of calcium salts used for hypocalcemic tetany, are described in the chapter on Agents Used in Metabolic Disorders. Preparations of plasma for intravenous injection to restore blood volume are to be found in the chapter on Serums and Vaccines.

Parenteral solutions are often warmed so that they may enter the vein at body temperature. The entire apparatus (bottle or flask, rubber tubing, connections, and needle) must be sterile and the entire line of rubber tubing, as well as the needle, must be freed of air bubbles before the needle is inserted. The area in which the needle is injected must also be adequately prepared. The intake air should be filtered by a cotton pledget or other adequate device.

The administration of these solutions should be instituted by a physician and continued under his supervision (especially intravenous injection), and must be discontinued before the container is empty. Intraperitoneal injections are not recommended because they cause distention which may be prolonged and may induce a sterile peritonitis with polymorphonuclear exudation.

Frequently apparatus used for the administration of intravenous solutions is used repeatedly. Before the apparatus is again used it must be sterilized, this sterilization process to be preceded by rinsing several times in distilled water. This should eliminate any untoward reactions which may be due to the lack of such thorough cleansing.

Many parenteral solutions are offered in special containers bearing special trademark designations. Most of these have been examined by the A. M. A. Chemical Laboratory and many formerly were described in New and Nonofficial Remedies. Included are containers bearing such names as "Vacoliter" (Baxter Laboratories, Inc. and Don Baxter, Inc.), "Saftiflask" (Cutter Laboratories), "Filtrair" (Hospital Liquids, Inc.).

SODIUM LACTATE

SODIUM LACTATE INJECTION-U. S. P.—A sterile solution of sodium lactate ($\text{NaC}_2\text{H}_3\text{O}_2$) in water for injection.

—It contains not less than 95 per cent and not more than 110 per cent of the labeled amount of $\text{NaC}_7\text{H}_5\text{O}_3$ —U S P

For tests and standards see the U S Pharmacopoeia under Sodium Lactate Injection

Actions and Uses—Sodium lactate injection is approximately isotonic with the blood and is used in the treatment of acidosis (as such or combined with Ringer's solution) and for the purpose of alkalizing the urine (for instance in the treatment of acute urinary tract infections with sulfanilamide, in the treatment of transfusion reactions with hemoglobinuria). This solution is not indicated in the acidosis associated with congenital heart disease with persistent cyanosis.

Dosage—Administered subcutaneously or intravenously. Intravenous solutions should not be administered at a rate greater than 300 cc per hour (approximately 60 drops per minute) except on specific order of the physician. It can be calculated that each 60 cc of sodium lactate injection per kilogram of body weight may increase the sodium ion concentration of the blood plasma about 14 millimols (mM) per liter. This corresponds to a rise in bicarbonate concentration sufficient to yield an additional 33 volumes of carbon dioxide per hundred cubic centimeters of blood plasma.

Pharmaceutic and Therapeutic Aids

This chapter contains substances which in themselves are essentially therapeutically inactive but which are nevertheless useful in the practice of medicine. Included are such articles as solvents, antioxidants, emulsifying agents, water-soluble bases, lubricants, and other materials such as dusting powder, vehicles, preservatives and protectives.

ABSORBABLE GELATIN SPONGE.—Gelfoam (UPJOHN).—A sterile absorbable water-insoluble gelatin base sponge.

For tests and standards, see Section B.

Actions and Uses.—Absorbable gelatin sponge material, although insoluble in aqueous mediums, is absorbable and as such may be used as a surgical sponge, which may be left in place following closure of an operative wound. It is claimed that such material will be completely absorbed without inducing excessive formation of scar tissue or excessive cellular reaction in from four to six weeks. It is indicated in the control of capillary bleeding, particularly when moistened with thrombin solution.

Dosage.—Absorbable gelatin sponge may be applied to the bleeding surfaces in amounts sufficient to cover the area. For such purposes it should first be moistened thoroughly with sterile isotonic sodium chloride solution or thrombin solution.

THE UPJOHN COMPANY

Gelfoam: Jars containing four sterile sections, 20 by 60 mm. and sterile envelopes containing a single section 80 by 125 mm.

CARBOWAX 1500 (CARBIDE & CARBON).—White grade.—A mixture of polyethylene glycols, having an average molecular weight of about 550, suitable for the compounding of water-soluble ointment bases. It is a bland, water-soluble, non-volatile, odorless solid, having the consistency of a low-melting petrolatum. It is insoluble in petroleum ether but completely soluble in water at 50 C. It melts from 30-42 C., and the pH of a 5 per cent aqueous solution is about 4.6.

Trademark of Carbide and Carbon Chemicals Corporation (U. S. trademark 380,450).

CARBOWAX 4000 (CARBIDE & CARBON)—A polyethylene glycol, having an average molecular weight of 3350. It is a bland hard white, waxy solid which melts from 54-57 C. It is soluble to form about 60 per cent solutions in water but is insoluble in petroleum ether. The pH of a 5 per cent solution is about 6.35. It is used in compounding water soluble ointment vehicles.

Trademark of Carbide and Carbon Chemicals Corporation (U. S. trademark 380 450).

CARBOWAX 1540 (CARBIDE & CARBON)—A polyethylene glycol having an average molecular weight of about 1450. It is a bland white waxy solid which melts from 40 to 45 C. It is soluble to form about 70 per cent solutions in water but is insoluble in petroleum ether. The pH of a 5 per cent solution is about 6.5. It is used in compounding water soluble ointment vehicles.

Trademark of Carbide and Carbon Chemicals Corporation (U. S. trademark 380 450).

FIBRIN FOAM—A sterile, dry preparation of fibrin prepared from Fraction I of citrated normal human plasma as fractionated by the method of Cohn (*J. Am. Chem. Soc.* 68 459, 1946). It complies with the requirements of the National Institute of Health of the United States Public Health Service.

For tests and standards see Section B.

Actions and Uses—Fibrin foam (human) acts as a mechanical coagulant and in combination with thrombin gives a chemical as well as a mechanical matrix for coagulation. It has been used in surgery of the brain, liver, kidneys, and other organs where ordinary methods of hemostasis are ineffective or inadvisable.

Dosage—Apply directly to oozing surface.

CUTLER LABORATORIES

Fibrin Foam and Thrombin (Human)—Packages containing a 250 mg. (6.25 to 12.55 cc.) jar of fibrin foam, a vial of thrombin (human) containing not less than 200 units, and a 20 cc. vial of isotonic sodium chloride solution.

The thrombin supplied meets the requirements of the National Institute of Health of the United States Public Health Service and is derived from human plasma.

Licensed by Research Corporation under U. S. patent 2,339,074.

GELATIN COMPOUND PHENOLIZED—A mixture composed of gelatin 14 per cent, carbolic acid (phenol) 1.5 per cent, zinc oxide 5.5 per cent and glycerin 39 per cent.

Actions and Uses—Gelatin compound phenolized is used in the preparation of bandages to cover chronic ulcers and unhealed secondary burns and in the preparation of pressure bandages for varicose veins when surgical treatment is not necessary.

Dosage—For use the preparation is heated until it becomes liquid and is applied with a brush over this a spiral bandage is applied and another layer of the preparation brushed on.

standard color. Marketed only in the form of Parresined Lace Mesh Surgical Dressing.

Actions, Uses and Dosage.—Nonabsorbent protective, used for the preparation of Parresined Lace Mesh Surgical Dressing.

ABBOTT LABORATORIES

Parresined Lace-Mesh Surgical Dressing: Net mesh gauze impregnated with, and containing, from 45 to 50 per cent of Parresine.

U. S. trademark 117,626.

POLYETHYLENE GLYCOL 300 (CARBIDE & CARBON).

—White grade.—A polymer having the general formula $\text{HOCH}_2(\text{CH}_2\text{OCH}_2)_n\text{CH}_2\text{OH}$, with an average molecular weight of 300. It is a white, viscous liquid, which freezes between -15 and 8°C . It is completely miscible with water in all proportions and is useful in the compounding of water soluble ointment bases and pharmaceuticals for topical applications.

PROPYLENE GLYCOL-N. F.—Racemic 1,2-dihydroxypropane— $\text{CH}_3\text{CHOHCH}_2\text{OH}$. "Contains not less than 97.5 per cent by weight of $\text{C}_3\text{H}_8\text{O}_2$ {propylene glycol}."—N. F.

For description and standards see The National Formulary under Propylene Glycol.

Actions and Uses.—Propylene glycol is used for pharmaceutical purposes as a diluent. Its toxicity is similar to that of glycerin. As ordinarily employed, it may be called practically nontoxic.

STARCH-DERIVATIVE DUSTING POWDER.—

Bio-Sorb (Etnicon).—A biologically absorbable powder prepared from cornstarch by etherification with epichlorohydrin. The starch polymer chains are presumably cross-linked by 1,3-diether glycerine group to the extent of not more than 2 per cent of the original starch weight. The starch derivative is mixed with magnesium oxide, 2 per cent, and small residual amounts of sodium sulfate and sodium chloride.

For tests and standards, see Section B.

Actions and Uses.—Starch derivative dusting powder is a light dusting powder suitable for use as a lubricant for the hands in donning rubber gloves and for other uses to which talcum powder is ordinarily applicable in general hospital routines. As a substitute for ordinary powdered talc, it has been shown to have the advantage of biologic absorbability and is thus comparatively nonirritating and nontoxic. Its use therefore avoids the known hazards of talcum powder.

Starch derivative dusting powder should be autoclaved for the purpose of sterilization. Slight clumping which occurs after repeated autoclaving may be readily broken up with moderate pressure. Dry wall heat sterilization is not recommended for bacteriologic reasons and should be avoided because of the possible

inflammability of the powder. However, even in contact with red hot cautery the powder will flash only to about the same degree as cotton, so that this property is not considered to constitute a hazard to its use in surgery.

Dosage—An amount just sufficient to lubricate the skin or article for which a dusting powder is indicated should be employed in the same manner as for the use of ordinary talc.

ETHICON SUTURE LABS

Bio Sorb (Powder) 227 Kg cans

U S trademark pending

THIOUREA— $S\ C(NH_2)_2$

For tests and standards see Section B

Uses—Thiourea may be added to solutions of certain substances e.g., Metycaine with epinephrine, in order to prevent oxidation.

TRIETHANOLAMINE U S P—A mixture of alkanol amines consisting largely of triethanolamine $N(C_2H_4OH)_3$ admixed with various amounts of diethanolamine $NH(C_2H_4OH)_2$ and monoethanolamine $NH_2(C_2H_4OH)$. It has an alkalinity equivalent to not less than 67 cc. and not more than 7.2 cc. of normal acid for each 1 Gm. of Triethanolamine.—
U S P

For description and standards see the U S Pharmacopeia under Triethanolamine.

Actions and Uses—Triethanolamine technical is an excellent emulsifying agent for use in the preparation of ointments and other dermatologic medicaments. When added to certain preparations used on the scalp for example oil of cade it facilitates their subsequent removal. Triethanolamine technical combines with fatty acids to form soaps with good detergent properties which are soluble not only in water but also in gasoline, kerosene and oils. It is claimed to have the power of increasing the penetration of oily substances and to possess a certain amount of bacteriostatic action. Rarely an individual will be encountered who is sensitive to this compound.

Dosage—In the preparation of stable emulsions of fatty or vegetable oils, triethanolamine and oleic acid are first added to about one third of the oil. Using mechanical agitation about one-third of the water is added and stirred until a thick smooth emulsion is formed. Then with continued mechanical agitation alternate thirds of oil and water are slowly stirred in. Emulsions may be made containing from 20-40 per cent of oil which may be diluted with as much as five times the volume of water. For emulsions containing olive oil the proportions based on the weight of the oil are 2.4 per cent by weight triethanolamine and 11.5 per cent oleic acid. Substantially the same proportions are used for the majority of vegetable oil emulsions while for paraffin oil emulsions the amount of triethanolamine should be increased to 5 per cent by weight.

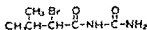
Sedatives and Hypnotics

This chapter includes agents that act principally as depressants of the central nervous system and that may be used to induce sleep if pain is absent or to control convulsions. This group is to be distinguished on the one hand from the analgesics which are used to relieve pain, and on the other hand from the antispasmodics which act primarily to depress muscular activity. Their distinction from anesthetics is less sharp since some sedative compounds, notably the barbiturates, may be administered in doses sufficient to produce general anesthesia. Morphine and its derivatives, used mainly as analgesics, are included along with opium principles in the chapter on Analgesics.

COMPOUNDS CONTAINING BROMINE

Synthetic compounds containing bromine have been produced with the purpose of securing the sedative action of bromide ion without the objectionable effects of the alkali bromides. These compounds split off bromide ions in the system, the decomposition being due to the oxidation of the organic substance with which it is combined; but bromine which is too firmly bound may fail to exert its typical effects. As the usual indications for bromide action in the organism require a prompt and powerful action on the cells to produce sleep, to abolish reflexes or to arrest an epileptic paroxysm, the synthetic compounds are likely to fail as substitutes for the alkali bromides because their bromide ion is liberated too slowly. The introduction of bromine into compounds already possessing hypnotic or sedative powers may result in increasing the efficiency of these compounds.

BROMISOVALUM—Bromural (BILHUBER-KNOLL).—2-Bromisovalerylurea, obtained by the interaction of urea with bromisovaleryl bromide. The formula may be represented as follows:



For tests and standards, see Section B.

Actions and Uses—Bromisovalum is a sedative which produces sleep in mild cases of insomnia without markedly affecting the circulation or respiration. All action by bromisovalum

is said to cease after from three to five hours. In many cases, however, the sleep caused by the preparation continues beyond the limits of its action. It is useful as a sedative and for the purpose of inducing sleep in functional nervous disease. Bromisovalum is not effective in cases of insomnia associated with pain, cough, angina pectoris or delirium.

Dosage—As a sedative 0.3 Gm. three times daily, as a hypnotic at bedtime, 0.6 Gm., which dose may be repeated if advisable during the night after three to four hours.

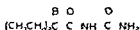
BILHUBER KNOLL CORP.

Tablets Bromural 0.3 Gm.

Bromural (*Powder*) 30 Gm. bottles

U. S. patent 914,518 (March 9, 1909, expired) U. S. trademark 61,163

CARBROMAL-N F—Bromodiethylacetylurea. The formula may be represented as follows:



For description and standards see The National Formulary under Carbromal.

Actions and Uses—Carbromal is said to be an efficient and prompt sedative, reducing excitement and promoting sleep in conditions in which a powerful hypnotic is not required. In therapeutic doses it is said not to exert any unfavorable influence on the respiration or heart action. The sleep produced is said to be restful, dreamless and exceptionally free from unpleasant by-effects and sequelae.

Carbromal is stated to be useful as a sedative and mild hypnotic in neurasthenia, cardiac neuroses with tachycardia, chorea, mental disorders with moderate excitement, insomnia due to various internal diseases.

Dosage—As a sedative from 0.3 to 0.6 Gm. given in cold water, repeated three or four times daily if necessary, as a hypnotic from 0.6 to 1.3 Gm., followed by a drink of hot, sweetened water or weak tea.

MERCK & CO., INC.

Carbromal (*Powder*)

THE UPJOHN COMPANY

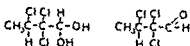
Tablets Carbromal 0.3 Gm.

CHLORAL DERIVATIVES

Chloral hydrate is still the standard hypnotic of its class, but it has the disadvantages of causing cardiac and respiratory depression in overdosage and of irritating the stomach unless

diluted :
 Attempt
 same tir
 to remo-
 chloral
 stomach. Chlorobutanol can be given by hypodermic injection.

structural formulas of b
 respectively, are given below.



For tests and standards, see Section B.

Actions and Uses.—The action of this preparation is similar to that of chloral hydrate.

Dosage.—From 0.3 to 1.3 Gm.

CHLOROBUTANOL-U. S. P.—Chloretone (PARKE, DAVIS).—"Chlorobutanol may be anhydrous or it may contain up to about one-half molecule of water." U. S. P. Its structural formula is



For description and standards see the U. S. Pharmacopeia under Chlorobutanol.

Actions and Uses.—Chlorobutanol is said to be absorbed unchanged from the alimentary tract, but to be decomposed in the body. It is a local anesthetic with an action weaker than that of cocaine, but sufficient action frequently to prevent vomiting from slight gastric irritation. Its antiseptic action is said to be fifteen times as strong as that of boric acid. It acts on the central nervous system

the claim has been made
 on the circulation and
 described a fall of blood pressure and interference with respiration in animals, and consider it fully as dangerous as chloral hydrate. In man 6.5 Gm (100 grains) caused severe symptoms, but recovery occurred. It is said to be useful as a mild local anesthetic in dentistry, etc., as a preservative for hypodermic solutions and for insomnia, vomiting and spasmodic conditions.

Dosage.—From 0.3 to 1.3 Gm., dry or in capsules. Hypodermically as a local anesthetic a saturated aqueous solution may be used.

MERCK & Co, INC.

Chlorobutanol (Hydrous Powder): Bulk. This product is used in the preparation of aqueous solutions

Chlorobutanol (Anhydrous Powder): Bulk. This product is used in the preparation of oil solutions

PARKE, DAVIS & COMPANY

Chloretone (Powder): Bulk.

Boro-Chloretone (Powder): A dusting powder composed of chloretone, 1 part, boric acid, 1 part, purified talc, 2 parts

Capsules Chloretone: 0.2 Gm. and 0.3 Gm

Inhalant Chloretone: Chlorobutanol, 1 Gm., camphor, 2.5 Gm.; menthol, 1.8 Gm.; oil of cinnamon, 60 mg.; refined liquid petrolatum, 94.64 Gm

U. S. trademark 175,422

HYDANTOIN DERIVATIVES

DIPHENYLHYDANTOIN SODIUM—U. S. P.—**Dilantin Sodium (PARKE, DAVIS)**—U. S. P.—5,5-Diphenylhydantoinate Sodium—Phenytoin Sodium.—“When dried at 100 C. for 4 hours, contains not less than 90.5 per cent and not more than 92 per cent of diphenylhydantoin ($C_{15}H_{12}N_2O_2$)” U. S. P. The formula may be represented as follows



For description and standards see the U. S. Pharmacopeia under Diphenylhydantoin Sodium and Diphenylhydantoin Sodium Capsules

Actions and Uses—Diphenylhydantoin sodium is an anticonvulsant with a relatively weak hypnotic action. It is used in the treatment of epileptic patients who are not benefited by phenobarbital or bromides and those in whom these drugs disagree.

It is also used in the treatment of nervousness, mental depression, and active hallucinations, and hyperplasia of the gums suggestive of scurvy, though its use does not interfere with the

utilization of vitamin C. Diphenylhydantoin sodium is strongly alkaline and it may give rise to gastric irritation.

Dosage.—The optimum dosage of diphenylhydantoin sodium must be determined by the daily observation of its effects by the physician. The influence of the drug on seizures and the appearance of any of the side actions enumerated must be a guide to the dosage. Mild symptoms do not necessarily require that the dosage be stopped. The beginning adult dose is 0.1 Gm. with at least half a glass of water three times daily. If necessary this dose may be increased gradually to 0.2 Gm. three times daily. Children above the age of 6 years may be given 0.1 Gm. three times daily for one week, after which it may be increased if necessary to 0.1 Gm. four times daily with at least half a glass of water to prevent gastric irritation due to the alkalinity. Diphenylhydantoin sodium is more rapidly effective if given before meals, but should it cause gastric irritation it should be given immediately after meals. Children under 4 years of age may start with 0.03 Gm. mixed with cream (to disguise the bitter taste and to prevent gastric irritation) twice a day. Obviously such doses require the most careful supervision. If this dose is borne without side actions the dosage may be increased to 0.03 Gm. three or four times a day. Every slight increase in dosage is made only after the physician is convinced that such

anticipated.

other hypnotic-
be made gradually with some overlapping in dosage. by this procedure the danger of phenobarbital or bromide withdrawal symptoms (increased number of seizures) is minimized, and side actions incident to the beginning administration of diphenylhydantoin sodium are lessened

AMERICAN PHARMACEUTICAL Co., INC.

Capsules Diphenylhydantoin Sodium: 0.1 Gm.

PARKE, DAVIS & COMPANY

Kapseals Dilantin Sodium: 0.1 Gm. and 30 mg

U. S. trademark applied for.

PREMO PHARMACEUTICAL LABORATORIES, INC.

Diphenylhydantoin Sodium (*Powder*): 28 Gm., 113 Gm. and 453 Gm. bottles.

Capsules Diphenylhydantoin Sodium: 30 mg and 0.1 Gm.

OXAZOLIDINE DERIVATIVES

TRIMETHADIONE (ABBOTT).—3,5,5-Tri-
ral formula of tri-



For tests and standards, see Section B

Actions and Uses—Trimethadione is primarily an anticonvulsant and has only minor analgesic properties. It is used in the treatment of epilepsy, in which it is principally effective in cases in which one of the two most common types of epilepsy, the grand mal, is not controlled by the usual anticonvulsants, sodium when the latter alone is ineffective. It may be tried in myoclonic and akinetic seizures of organic origin but is generally less effective than in the idiopathic forms of the disease. It has been used with diphenyl hydantoin sodium and/or phenobarbital in cases in which attacks are complicated by grand mal seizures. In some instances, the combination of drugs has served to increase the number of grand mal attacks as the petit mal has decreased and readjustment of dosage may be required for optimum therapeutic effect.

Trimethadione is contraindicated in patients with severe hepatic disease, severe renal disease, severe heart disease, severe pulmonary disease, severe hypotension, severe hypoglycemia, severe hypocalcemia, severe hypomagnesemia, severe hypokalemia, severe hypophosphatemia, severe hypovolemia, severe hypothermia, severe hypoxia, severe hypotension, severe hypoglycemia, severe hypocalcemia, severe hypomagnesemia, severe hypokalemia, severe hypophosphatemia, severe hypovolemia, severe hypothermia, severe hypoxia.

Phenobarbital is contraindicated in patients with severe hepatic disease, severe renal disease, severe heart disease, severe pulmonary disease, severe hypotension, severe hypoglycemia, severe hypocalcemia, severe hypomagnesemia, severe hypokalemia, severe hypophosphatemia, severe hypovolemia, severe hypothermia, severe hypoxia.

to report at once any untoward symptoms that may ensue. Careful medical supervision of patients under treatment with Trimethadione is essential.

ABBOTT LABORATORIES

Capsules Tridione 0.3 Gm

Dulcet Tablets Tridione 0.15 Gm.

U. S. trademark 500 527

Solution Tridione: 0.15 Gm. per 4 cc., 500 cc. and 4,000 cc. bottles.

U. S. trademark 500,401.

SULFONMETHANES

Two analogous compounds formed by the substitution of sulfone radicals in methane have been applied in therapeutics. The first, sulfonmethane, N. F. (sulfonmethane) is dimethylmethane is diethylsulfo-
erally given the preference.

Sulfonmethane is soluble with difficulty and slowly absorbed and its hypnotic action is but slowly established; sulfonethylmethane is somewhat more soluble than sulfonal and acts more quickly. Both drugs are preferably given in hot liquids; and in the case of sulfonmethane, the hypnotic effect is likely to be postponed for several hours. Sometimes it is not developed until the following day. Sulfonethylmethane is usually effective in an hour or two.

The sulfonmethanes in therapeutic doses produce sleep without noticeable effect.

tatally in a large percentage of cases. In such cases, hematomporphyrin derived from hemoglobin turns the urine pink or red. This should serve as a warning, indicating the immediate withdrawal of the drug.

The symptoms of poisoning consist of persisting confusion, ataxia, constipation, vomiting, albuminuria and nephritis.

Dosage.—The usual dose of either sulfonmethane or sulfonethylmethane is 1.0 Gm. with a maximum of 2 Gm. for the first and 4 Gm. for the second. When these drugs are used frequently, the administration should be suspended once in two or three days to allow of complete elimination, and the urine should be examined frequently for hematomporphyrin

SULFONETHYLMETHANE—*N. F.*—Diethylsulfomethylethylmethane—The structural formula may be represented as follows:



For description and standards see The National Formulary under Sulfonethylmethane.

Actions, Uses and Dosage.—See general article, Sulfonmethanes.

SULFONMETHANE—N F—Sulfonal—The structural formula may be represented as follows



For description and standards see The National Formulary under Sulfonmethane

Actions, Uses and Dosage—See general article, Sulfonmethanes

BARBITURIC ACID DERIVATIVES

Barbituric acid is a cyclic compound obtained by the combination of urea and malonic acid, and is also called malonyl urea.



It may exist in the 'keto' form represented above, or in the 'enol' form shown below. The latter form is derived by the migration of a hydrogen atom from the nitrogen atom in position 1 (or 3) to the oxygen attached to the carbon in position 2.



This form is acidic in nature the migrant H atom ionizing to produce a hydrogen ion and a barbiturate ion, and allows the formation of metallic salts.

Barbituric acid itself does not possess hypnotic properties. These are conferred when the hydrogens on carbon in the 5-

position are substituted for the radicals. Most of the clinically used hypnotics substituting for the radicals Phenobarbital contains an aromatic radical. Other variations in structure include the substitution of hydrogen for one or more of the hydrogens attached to the nitrogen atoms.

The following compounds and their salts are described in N N R.

DURATION OF ACTION	COMPOUNDS	SUBSTITUENTS		
		R ₁	R ₂	Other
Long	Barbital	Ethyl	Ethyl	
Long	Phenobarbital	Ethyl	Phenyl	
Intermediate	Alurate	Allyl	Isopropyl	
Intermediate	Butisol Sodium	Ethyl	1-Methylpropyl	
Intermediate	Delvinol	Ethyl	1-Methyl-1 butenyl	
Intermediate	Dial	Allyl	Allyl	
Intermediate	Ipral	Ethyl	Isopropyl	
Intermediate	Neonal	Ethyl	n-Butyl	
Short	Amytal	Ethyl	Isoamyl	
Short	Nostal	β -Bromallyl	Isopropyl	
Short	Ortal	Ethyl	n-Hexyl	
Short	Pentobarbital	Ethyl	1-Methylbutyl	
Short	Pernoston	β -Bromallyl	Butyl	
Short	Phanodorn	Ethyl	Cyclohexenyl	
Short	Sandoptal	Allyl	Isobutyl	
Short	Seconal	Allyl	1-Methylbutyl	
Ultrashort	Evipal	Methyl	Cyclohexenyl	1-Methyl
Ultrashort	Pentothal	Ethyl	1-Methylbutyl	2-Thio

Actions and Uses.—The derivatives of barbituric acid are ef-

peutic effects are exerted on the higher centers of the brain, and therapeutic doses do not usually cause any apparent injury to the vital organs.

The barbiturates are often classified according to their duration of action, as long, intermediate, short, and ultra-short-acting drugs. In general, the interval between the administration of the drug and the exhibition of its therapeutic effect corresponds to this classification; i.e., the short-acting drugs take effect rapidly, the long-acting drugs take effect slowly. For prolonged mild sedation in such conditions as neurasthenia and thyroid disease, and to reduce the frequency of epileptic convulsions, small doses of a long-acting barbiturate are useful. The effects of the individual doses overlap and produce a rather evenly maintained sedation.

Simple insomnia can be divided into two categories: one in which there is difficulty in falling asleep, but once sleep is achieved, it is undisturbed; the other in which sleep comes easily but is disturbed by nocturnal or very early morning awakening. For insomnia of the first type the drug of choice is *Barbital*, which produces sleep within one-
within four to six hours.
the drug of choice is an
effect comes on later and
duced by small doses of

these drugs closely resembles natural sleep, and the patient generally awakens refreshed.

There is a fairly wide margin between the therapeutic and toxic doses of barbiturates now in clinical use. Occasionally, however, even after moderate doses, lassitude, vertigo, headache, nausea and diarrhea may occur. In some patients the barbiturates produce restlessness and excitement, and the use of these drugs is contraindicated in such patients. Excitement and restlessness are prone to occur when the barbiturates are administered to patients in severe pain. The mechanism of action in this instance is that the drug does not relieve the pain but depresses the higher centers which normally act as inhibitors. Fairly typical skin eruptions are sometimes observed, especially after prolonged administration. Long continued use may result in addiction.

The long acting barbiturates are largely excreted by the kidney; the short acting barbiturates are destroyed to a large extent in the liver. The fate of pentothal in the body has been a matter of controversy but recent evidence indicates that it, too, is destroyed in the liver. The slower the excretion or destruction of the various members of this group the more lasting is the action. With very slow excretion, prolonged administration of ordinary doses may result in cumulative toxic effects. This must be borne in mind especially when the drugs are administered to patients with damaged liver or kidneys.

Poisoning with the barbiturates is a rather common occurrence, both accidentally and with suicidal intent. The toxic effects of overdosage are respiratory depression, peripheral vascular collapse, feeble heart beat, lowered body temperature, and long continued stupor with depressed or absent reflexes. Death results from depression or paralysis of the respiration or from pulmonary complications.

In the treatment of barbiturate poisoning the respiration and during the phase of depressed breathing the cardiovascular system should be supported by intravenous infusions of saline or

. frequently in order to prevent Analeptic drugs may be administered in small doses when there is deep coma and severe respiratory depression. These should be given until the respiration improves and the corneal reflex returns.

The barbiturates are commonly used for pre-anesthetic medication, either alone or in combination with other drugs. A short or intermediate acting drug is administered on the evening before operation to reduce apprehension and provide a

restful sleep. From one to two hours before operation a short-acting barbiturate is administered, often with morphine and atropine. The barbiturates are particularly valuable for premedication when a local or regional anesthetic is to be administered, since they reduce the frequency and severity of toxic reactions to the local anesthetic drugs.

Barbiturates are valuable in the treatment of convulsions resulting from local anesthetic drugs as well as in the treatment of convulsions from most other causes. The cautious intravenous administration of a short or ultrashort-acting barbiturate is usually very satisfactory in stopping a severe convulsion. For long continued control of convulsions, as in tetanus, the drugs may be given rectally as described below under basal narcosis.

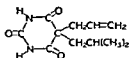
The barbiturates are useful in controlling excitement and manic states. Prolonged sleep induced by the barbiturates has been found useful in the treatment of psychic casualties of warfare. The intravenous barbiturates have also been found useful in the procedure of narco-analysis. A psychiatric interview is conducted while the patient is in a semiconscious state produced by small doses of drug. Therapy of some mental disorders is rendered easier by this procedure.

The barbiturates are also used in the control of pain during labor, either alone, or in combination with scopolamine to produce a form of twilight sleep. A frequent complication in this procedure is delirium and excitement of the mother, caused by pain which the barbiturates do not relieve. Amnesia may be achieved with moderate doses. The newborn infant is also affected by the drug given to the mother. In any large series of cases there is an increase in the incidence of delayed respiration, and more of the infants require resuscitation. The harmful

anesthesia because serious or fatal complications may occur even during a minor procedure. The drugs should be administered in a 25 per cent solution or less, to avoid the possibility of venous thrombosis. Induction is rapid and pleasant. Respiratory depression and apnoea are serious complications which may occur. The anesthetist must be capable of treating these and must have equipment at hand to give artificial respiration with oxygen. Laryngospasm and vomiting may occur but are not frequent. These drugs are contraindicated in shock or in operative procedures where shock may be expected. They are also contraindicated in patients with diminished pulmonary ventilation or respiratory obstruction, and in operations about the mouth and nose which may cause blood to run down the respiratory tract. Muscular relaxation with these drugs is poor, and attempts to increase the relaxation result in overdosage.

The intravenous barbiturates are of value for induction of anesthesia and for short operations which do not require muscular relaxation. Oxygen should be given during the procedure. Mixtures of 50 per cent nitrous oxide and oxygen may advantageously be administered to improve the anesthesia and reduce the amount of barbiturate used. Curare may be given to produce muscular relaxation during barbiturate anesthesia. The intravenous barbiturates are deceptively easy to administer, and caution must be exercised to prevent the occurrence of a catastrophe.

Basal narcosis may be produced by the rectal administration of short or ultrashort acting barbiturates. The drug is dissolved in a small volume of warm tap water and administered as a retention enema. Sleep is produced in about ten minutes. Short minor operative procedures may be performed without further anesthesia but for most operations the basal narcosis must be supplemented with one of the other anesthetic drugs. This method is particularly valuable for quiet induction of anesthesia in apprehensive children and in toxic thyroid patients. Pentothal sodium may be used in this manner in a dosage of 20 mg per pound (450 Gm) of body weight, the total dose not to exceed 3 Gm. Prolonged convulsive states as in tetanus may be controlled in this manner with reduced dosage. The precautions necessary with this method are the



For tests and standards see Section B

Actions and Uses—The same as those of barbital and its therapeutically useful derivatives

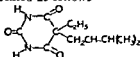
Dosage—For mild insomnia, 0.2 Gm for use in obstinate cases of insomnia, 0.4 to 0.8 Gm.

SANDOZ CHEMICAL WORKS INC.

Tablets Sandoptal 0.2 Gm.

U S trademark 234 623

AMOBARBITAL—Amytal (Lilly)—5 Isoamyl 5-ethyl barbituric acid—Isoamylethylmalonylurea. The structural formula may be represented as follows



For tests and standards, see Section B.

Actions and Uses—The actions and uses of amobarbital resemble those of barbitol. It is used as a sedative and hypnotic in the control of insomnia and as a preliminary to surgical anesthesia.

Dosage.—It is given orally in tablet form with water or hot milk. As a sedative: 20 mg. to 40 mg. two or three times daily. As a hypnotic: 0.1 to 0.3 Gm. one-half to one hour before sleep is desired. For use before local or general anesthesia the dosage ranges between 0.2 and 0.6 Gm., being determined by a large number of factors (age, etc.). It can be used safely for such purposes only by those who have had much experience and are familiar with the literature concerning such use. As an antispasmodic in tetanus, 0.4 to 0.8 Gm. may be required to control convulsions.

ELI LILLY AND COMPANY

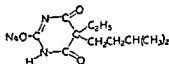
Amytal (Powder): Bulk.

Elixir Amytal: 0.44 Gm. per 100 cc. and 0.88 Gm. per 100 cc. in a vehicle containing methenamine 0.416 Gm. and 0.83 Gm. per 100 cc. respectively, alcohol, propylene glycol, water and aromatics; methenamine is present for the purpose of increasing the solubility of the amobarbital.

Tablets Amytal: 8 mg., 16 mg., 32 mg., 48 mg. and 96 mg.

U. S. patent 1,514,573 (Nov. 4, 1924; expired). U. S. trademark 161,125.

AMOBARBITAL SODIUM.—Amytal Sodium (LILLY).
salt of 5-la may be



For tests and standards, see Section B.

Dosage—As a potent sedative or hypnotic 65 mg. to 0.5 Gm., repeated if necessary at intervals of six hours. For use before local or general anesthesia the dosage ranges between 0.2 and 0.6 Gm., being determined by a large number of factors (age, etc.). For use before tetanus from 0.4 to 0.8 Gm. may be used safely for such purposes only by those who have had much experience and are familiar with the literature concerning such use. In some patients with nervousness and excitement, and to these patients amobarbital sodium should not be adminis-

tered. It may be administered by mouth, or, if necessary, the same dose may be given rectally, in the form of capsules inserted as suppositories or as powder placed in a little water, it should be administered intravenously only in those conditions outlined in the general section on barbituric acid derivatives. The maximum single dose of 1 Gm should not be used except when an intense and prolonged effect is desired. Usually no more than 1 Gm will be necessary in a 24 hour period.

ELI LILLY AND COMPANY

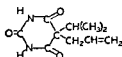
Amytal Sodium (Powder): 30 cc

Pulvules Amytal Sodium: 0.2 Gm and 0.1 Gm

Amytal Sodium: 65 mg, 0.125 Gm, 0.25 Gm, 0.5 Gm and 1.0 Gm ampuls. Each ampul of 0.25 Gm, 0.5 Gm and 1.0 Gm is accompanied by an ampul of distilled water.

Suppositories Amytal Sodium: 0.2 Gm

U S patent 1,514,573 (Nov. 4, 1924, expired) U S trademark 161,125



For tests and standards, see Section B

Actions and Uses—The actions and uses of aprobarbital are essentially similar to those of barbital, but aprobarbital is more active than barbital and is used in correspondingly smaller doses. Fractional doses are used as a sedative and larger doses as a hypnotic.

Dosage—For mild cases of insomnia, 65 mg may be administered at bedtime. In obstinate cases, 0.13 Gm may be given.

HOFFMANN-LA ROCHE, INC.

Alurate (Powder): Bulk

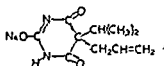
Elixir Alurate: Contains aprobarbital approximately 0.9 Gm per hundred cubic centimeters in a palatable elixir containing alcohol 20 per cent.

U S patent 1,444,802 (Feb. 13, 1923, expired) U S trademark 230,059

Tablets Alurate: 65 mg

APROBARBITAL SODIUM—Alurate Sodium (HOFFMANN-LA ROCHE)—Sodium 5-allyl 5-isopropyl barbiturate. The

monosodium salt of 5-allyl-5-isopropyl malonylurea. Its structural formula may be represented as follows:



For tests and standards, see Section B.

Actions and Uses.—The same as those for aprobarbital. The soluble sodium salt is intended for oral or rectal administration, particularly as pre-anesthesia medication. Aprobarbital sodium also be used in other cases in which large individual doses are required.

Dosage.—The average preoperative dose is 10 mg. per kilogram of body weight. One third of the calculated dose is given ten or twelve hours prior to operation (usually the evening before); the remainder, two hours before operation. Experience is necessary in the use of these large dosages, as the amount of the drug must be adjusted to the individual patient in order to avoid undesirable reactions.

HOFFMANN-LA ROCHE, INC.

Capsules Alurate Sodium; .227 Gm. Each capsule is equivalent to approximately 0.2 Gm. of aprobarbital

U. S. patent 1,444,802 (Feb. 13, 1923; expired). U. S. trademark 230,059.

BARBITAL-U. S. P.—Veronal (WINTHROP-STEARNES).—Diethylbarbituric Acid.—Barbitone.—Diethylmalonylurea The structural formula may be represented as follows:



For description and standards see the U. S. Pharmacopeia under Barbital and Barbital Tablets and The National Formulary under Barbital Elixir.

Actions and Uses.—See the general article, Barbituric Acid Derivatives. Barbital is quickly absorbed, especially when it is given in solution. Small doses induce sleep, apparently with little other effect, and are relatively safe; but fatalities have followed its indiscriminate use.

Dosage.—As hypnotic, 0.3 Gm., best prescribed in the form of powder to be given in hot fluid, such as hot milk, half an hour or an hour before bedtime. Pills or tablets should be crushed before swallowing, to insure absorption. From 0.1 to 0.15 Gm. are used with analgetics for the relief of pain.

ABBOTT LABORATORIES

Tablets Barbitol: 0.3 Gm

MALLINCKRODT CHEMICAL WORKS

Barbital (*Powder*): Bulk

MERCK & Co, INC.

Barbital (*Powder*): Bulk

Tablets Barbitol: 0.3 Gm

WINTHROP STEARNS, INC

Veronal (*Powder*): Bulk

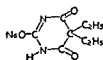
Elixir Veronal: Each 4 cc contains barbitol 0.13 Gm in a menstruum containing alcohol 33.5 per cent

Tablets Veronal 0.3 Gm

U S patent 782,739 (Feb 14, 1905, expired) U S trademark 40,115

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For description and standards see the U S Pharmacopeia under Barbitol Sodium and Barbitol Sodium Tablets

Actions and Uses—The same as those of barbitol. It is claimed, however, that this drug acts more rapidly on account of its greater solubility. Because of its solubility, administration by rectal injection and also subcutaneous injection has been proposed.

Dosage—The same as that of barbitol. It should be administered in aqueous solution.

MERCK & Co, INC.

Barbitol Sodium (*Powder*): Bulk.

Tablets Barbitol Sodium: 0.3 Gm

SCHERING & GLATZ, DIVISION OF WM. R. WARNER & Co, INC.

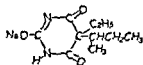
Medinal (*Powder*): 30 Gm bottles

Elixir Medinal: 180 cc. and 3.79 liters. A solution containing in each 4 cc., 0.12 Gm. medinal in 20 per cent alcohol.

Tablets Medinal: 0.3 Gm.

U. S. patents 780,241 (Jan. 17, 1905; expired) and 879,499 (Feb. 19, 1908; expired). U. S. trademark 269,753.

BUTABARBITAL SODIUM, Butisol Sodium (Mc.



For tests and standards, see Section B.

Actions and Uses.—Butabarbital sodium produces pharmacologic actions similar to other barbiturates. With average doses the rapidity and duration of its action is intermediate between the fast-acting derivative, pentobarbital, and the longer-acting barbital and phenobarbital. Following oral administration the drug usually exerts initial effects within 30 minutes. Sedation is sustained for approximately five to six hours. It is thus suited for the production of a relatively mild and more continuous depression than can be obtained with the shorter-acting barbiturates, yet its action is less prolonged than with barbital or phenobarbital.

Butabarbital sodium is destroyed fairly rapidly in the body, probably in the liver. It is not excreted as such in the urine except with excessive doses and therefore is not contraindicated in the presence of renal disease. Experimental studies indicate it to be essentially nontoxic for the liver. Its therapeutic coefficient is approximately equal to that of pentobarbital and greater than that of phenobarbital.

Butabarbital sodium is used orally as a simple sedative or hypnotic and for pre-operative sedation and obstetric hypnosis. Essentially the same clinical precautions to avoid side effects should be observed as for other barbiturates.

Dosage.—Orally: sedative, 8 to 60 mg.; hypnotic, 45 mg to 0.2 Gm., depending on the purpose and the patient. In general the duration of action is dependent on the size of the dose and the size of the patient. The average oral adult sedative dose is 30 mg.; the average hypnotic dose, 0.1 Gm.

McNEIL LABORATORIES, INC.

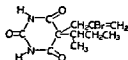
Capsules Butisol Sodium: 0.1 Gm.

Elixir Butisol Sodium: 0.2 Gm per 30 cc. butabarbital sodium dissolved in a flavored elixir containing 7 per cent alcohol.

Tablets Butisol Sodium 15 mg and 50 mg

U S trademark 378 610

BUTALLYLONAL — Pernoston (AMES) — 5 sec Butyl 5 β bromallylbarbituric acid — 5 (butyl 2) 5 β brompropenylmalonylurea The structural formula may be represented as follows



For tests and standards see Section B

Actions and Uses — The actions and uses of butallylonal are essentially similar to those of barbital but butallylonal is more active than barbital and is used in correspondingly smaller doses. It is promptly absorbed and is rapidly changed and destroyed within the body. It is used in combating insomnia due to emotional strain and nervous instability.

Dosage — One tablet (194 mg) given one half hour before sleep is desired preferably followed by a glass of warm milk or lemonade. For hypnosis in the presence of pain one tablet given in conjunction with acetylsalicylic acid.

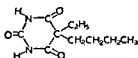
AMES COMPANY INC.

Pernoston (Powder) Bulk

Tablets Pernoston 194 mg

U S patent 1 739 662 (Dec 17 1929 exp red 1946) U S trademark 330 845

BUTETHAL — Neonal (ABBOTT) — 5 n Butyl 5 ethylbarbituric acid — 5 n butyl 5 ethylmalonylurea The structural formula may be represented as follows



For tests and standards see Section B

Actions and Uses — The actions and uses of butethal are essentially similar to those of barbital, but it is about three times

more is required

Dosage — From 50 mg to 0.4 Gm. For mild insomnias 50 mg

to 0.1 Gm. is stated ordinarily to produce sleep. A dose of 0.4 Gm. is the maximum dose which should be required in the course of twenty-four hours, administered in divided doses.

ABBOTT LABORATORIES

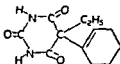
Neonal (Powder): Bulk.

Tablets Neonal: 0.1 Gm

U. S. patent 1,609,520 (Dec. 7, 1926; expired). U. S. trademark 175,580.

CYCLOBARBITAL

follows:



For tests and standards, see Section B

Actions and Uses.—The actions and uses of cyclobarbital resemble those of barbital. It is eliminated more rapidly than barbital; hence the action is not so lasting. This is an advantage when it is used merely to put one to sleep and sleep will then continue without its further action. It is used mainly for its sedative action in neurasthenia, psychoses, and various types of insomnia.

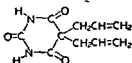
Dosage.—For the mildest type of simple insomnia, 0.1 Gm. or $\frac{1}{2}$ tablet. In intractable or obstinate insomnia, from 0.2 to 0.4 Gm. or one to two tablets. The larger dose should not be repeated within less than twelve hours. The average dose is 0.2 Gm. or one tablet.

WINTHROP-STEARNES, INC.

Tablets Phanodorn: 0.2 Gm.

U. S. patent 1,690,796 (Nov. 6, 1928; expired).

Diallylbarbituric Acid (CIBA).—5,5-
The structural



For tests and standards, see Section B.

Actions and Uses.—The actions and uses of diallylbarbituric

acid are essentially similar to those of barbital but diallylbarbituric acid is more active than barbital and it is used in correspondingly smaller doses. Fractional doses are used as a sedative and larger doses as a hypnotic. Therapeutic doses act on the higher centers of the brain and exert no injurious action on respiration or circulation. The hypnotic action is induced within from one half to one hour.

The actions and uses of diallylbarbituric acid with urethane are the same as those of diallylbarbituric acid. It is claimed that the ethyl carbamate and monoethylurea are used as solvents and in the amounts present do not greatly affect the action of the diallylbarbituric acid content. Solution diallylbarbituric acid with urethane is proposed for intramuscular administration and in the case of a pressing emergency only for intravenous injection. The solution being strongly hypertonic, subcutaneous injection should never be employed.

Dosage—As a sedative 30 mg. three or four times daily. As a hypnotic 0.1 to 0.3 Gm. one half to one hour before sleep is desired.

CIBA PHARMACEUTICAL PRODUCTS INC.

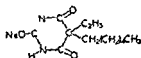
Dial (Powder) 10 Gm. and 30 Gm.

Elixir Dial Each 4 cc. contains 50 mg. in a menstruum containing alcohol 25 per cent.

Solution Dial with Urethane 1 cc. and 2 cc. ampuls. Each cc. contains diallylbarbituric acid 0.1 Gm. ethyl carbamate (urethane) 0.4 Gm. monoethylurea 0.4 Gm. and water q. s.

Tablets Dial 30 mg. and 0.1 Gm.

U. S. patent 1,042,765 (Oct. 22, 1912 expired) U. S. trademark 98,204 and 1,6088



For tests and standards see Section B.

Actions and Uses—The actions and uses of hexethal sodium are essentially similar to those of barbital but hexethal sodium is more active than barbital and it is used in correspondingly smaller doses.

Dosage—From 0.2 to 0.4 Gm. followed by a glass of water. It is rarely necessary to give more than 1 Gm. in 24 hours.

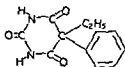
ELI LILLY & COMPANY

Pentobarbital-Sodium: 0.5 Gm, marketed in ampuls with or without a 10 cc. size ampul of distilled water.

PREMO PHARMACEUTICAL LABORATORIES, INC.

Solution Pentobarbital Sodium: 0.1625 Gm pentobarbital sodium and benzyl alcohol 2 per cent in propylene glycol per cc., 1 cc. and 2 cc. ampuls.

PHENOBARBITAL-U. S. P.—Luminal (WINTHROP-STEARNs). — Phenylethylmalonylurea. — Phenobarbitone. The structural formula may be represented as follows:



For description and standards see the U. S. Pharmacopeia under Phenobarbital, Phenobarbital Tablets, and Phenobarbital Elixir.

Actions and Uses—The introduction of the phenyl group increases the hypnotic effect of phenobarbital over barbital. The duration of action is increased in about 50 per cent, and the period of excitement is lessened.

Moderately large therapeutic doses sometimes cause severe circulatory depression. Habit formation has been reported.

Phenobarbital has a sedative action on respiration, lessening the frequency of breathing. It is eliminated by the kidneys, a certain portion being probably decomposed in the organism. No gastric disturbances have been observed.

Phenobarbital is used as a useful hypnotic in nervous insomnia and conditions of excitement of the nervous system, its chief use in this field is as a sedative, and as an antispasmodic in the treatment of epilepsy, in which it lessens the frequency and severity of seizures. Its use as a sedative has also been proposed in chorea, neurasthenia, cardiac and gastric neuroses, climacteric disorders, dysmenorrhea, exophthalmic goiter, and preoperative and postoperative cases.

Dosage.—From 15 mg. to 0.2 Gm increased if necessary to 0.6 Gm. The average dose is 0.1 Gm. A maximum dose of 0.6 Gm. should not be exceeded.

ABBOTT LABORATORIES

Phenobarbital (Powder): Bulk.

Tablets Phenobarbital: 16 mg., 32.5 mg., 0.1 Gm.

AMERICAN PHARMACEUTICAL COMPANY, INC.

Tablets Phenobarbital: 32 mg., 16 mg. and 0.1 Gm.

GEORGE A. BREON & COMPANY INC.

Tablets Phenobarbital 32.4 mg and 109 mg

BUFFINGTON S. INC.

Tablets Phenobarbital 16 mg 32 mg and 0.1 Gm

FLINT EATON & COMPANY

Tablets Phenobarbital 16 mg 32 mg and 0.1 Gm

GANE AND INGRAM INC.

Phenobarbital (*Powder*) Bulk

THE HARROWER LABORATORY INC.

Tablets Phenobarbital 32 mg

MERCK & CO. INC.

Phenobarbital (*Powder*) Bulk.

THE WM. S. MERRELL COMPANY

Tablets Phenobarbital 15 mg 30 mg 100 mg

E. S. MILLER LABORATORIES INC.

Tablets Phenobarbital 15 mg 30 mg and 100 mg

SMITH DORSEY COMPANY

Tablets Phenobarbital 8 mg 16 mg 32.5 mg and 0.1 Gm

THE UPJOHN COMPANY

Tablets Phenobarbital 16 mg 32.5 mg 0.1 Gm

THE VALE CHEMICAL CO. INC.

Tablets Phenobarbital 15 mg 30 mg and 0.1 Gm

WARREN TEED PRODUCTS COMPANY

Tablets Phenobarbital 16 mg 32.5 mg 0.1 Gm

WINTHROP STEARNS INC.

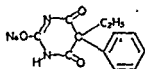
Luminal (*Powder*) Bulk.

Elixir Luminal Each 4 cc. contains 16.2 mg in a menstruum containing alcohol 26 per cent.

Tablets Luminal 16.2 mg 32.4 mg and 109 mg

U. S. patent 1,025,872 (May 7, 1912 exp. red.) U. S. trademark 87,327

culated on a moisture free basis corresponding to not less than 98.5 per cent of $C_{12}H_{11}N_2O_3Na$ U. S. P. The structural formula may be represented as follows



For description and standards see the U. S. Pharmacopeia under Phenobarbital Sodium and Phenobarbital Sodium Tablets.

Actions and Uses. that it may be administered are not produced on oral administration.

Dosage. For hypodermic injection, phenobarbital sodium is used in the form of a 1% solution in propylene glycol. The dissolving of the solution is complete. ly in doses of 0.1 to 0.3 Gm.

Caution: Aqueous solutions of phenobarbital sodium are not stable but decompose on standing; on boiling, precipitation occurs.

ABBOTT LABORATORIES

Phenobarbital Sodium (*Powder*): Bulk.

Phenobarbital Sodium (*Powder*): 0.13 Gm. ampuls.

Phenobarbital Sodium (*Powder*): 0.324 Gm., 2 cc. ampuls

Tablets Phenobarbital Sodium: 65 mg. (hypodermic) and 0.1 Gm.

ENDO PRODUCTS, INC.

Sodium Phenobarbital Solution in Propylene Glycol: 0.16 Gm. and 0.325 Gm., 2 cc. ampuls.

GANE AND INGRAM, INC.

Phenobarbital Sodium (*Powder*): 30 cc., 60 cc. and 120 cc. bottles.

Tablets Phenobarbital Sodium: 109 mg.

MALLINCKRODT CHEMICAL WORKS

Phenobarbital Sodium (*Powder*): Bulk.

MERCK & Co., INC.

Phenobarbital Sodium (*Powder*): Bulk.

THE WM. S. MERRELL COMPANY

Solution Phenobarbital Sodium with Benzyl Alcohol 2% in Propylene Glycol 70%: 0.12 Gm. and 0.3 Gm., 2 cc. ampuls.

WARREN TEED PRODUCTS COMPANY

Solution Phenobarbital Sodium with Benzyl Alcohol
2% in Propylene Glycol 0.12 Gm per cc 1 cc ampuls

WINTHROP STEARNS INC

Luminal Sodium (Powder) Bulk.

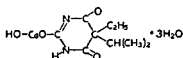
Solution Luminal Sodium in Propylene Glycol Phenobarbital sodium 0.16 Gm dissolved in propylene glycol per cc 2 cc. ampuls The solution may be administered intramuscularly or subcutaneously but not intravenously

Luminal Sodium (Powder) 130 mg and 324 mg ampuls

Tablets Luminal Sodium 15 mg 30 mg and 100 mg and 60 mg (hypodermic)

U S patent 1 025 872 (May 7 1912 exp red) U S trademark 87 327

PROBARBITAL CALCIUM.—Ipral Calcium (SQUIBB)
—Calcium 5 ethyl 5 isopropylbarbiturate—The trihydrated calcium salt of 5 ethyl 5 isopropylmalonyl urea The structural formula may be represented as follows



For tests and standards see Sect on B

Actions and Uses—Probarbital calcium has the therapeutic properties of barbituric acid. It is soluble in water and is absorbed promptly. It is claimed that it is excreted rapidly but some action commonly persists for twenty four hours.

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might succeeding that when the hypnotic was administered.

The drug should be administered sparingly to patients in whom the proposed operation may lead to circulatory collapse and shock. For severe trauma or in the presence of shock the drug should not be administered. It is also contraindicated in patients with pulmonary disease and pulmonary edema and in cases of uncontrolled diabetes.

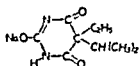
Dosage—As a sedative 0.13 to 0.26 Gm hypnotic 0.26 to 0.39 Gm preoperative 0.52 Gm postoperative 0.05 Gm. From 0.12 to 0.25 Gm followed by a cupful of hot water tea or milk. For pre anesthetic sedation the recommended dose is 0.25 to 0.5 Gm.

Caution Aqueous solutions of probarbital salts are not stable but decompose on standing on boiling precipitation occurs.

E. R. SQUIBB & SONS

Tablets Ipral Calcium: 50 mg. and 0.13 Gm.

U. S. patents 1,255,951 and 1,576,014 U. S. trademark 208,813.

(SQUIBB).—
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For tests and standards, see Section B.

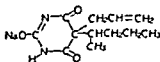
Actions, Uses and Dosage.—See monograph on Probarbital Calcium.

E. R. SQUIBB & SONS

Elixir Ipral Sodium: 6.15 Gm. in 473 cc., 5 cc. is equivalent to 65 mg. of Ipral Sodium.

Tablets Ipral Sodium: 0.26 Gm.

U. S. patents 1,255,951 (Feb. 12, 1918; expired); and 1,576,014 (March 9, 1926; expired). U. S. trademark 208,813.

SECONAL SODIUM (Lilly).—Sodium 5-allyl-5-(1-methylbutyl)barbiturate. The structural formula may be represented as follows:

For tests and standards, see Section B.

Actions and Uses.—The actions and uses of this barbiturate are essentially those of barbitol but it is described as a short-acting barbiturate. It is more active than barbitol and is used in correspondingly smaller doses.*Dosage.*—The average adult dose is from 0.1 to 0.2 Gm.

0.1 Gm. to 0.2 Gm. doses at appropriate intervals up to a total of no more than 1.2 Gm. within a 12 hour period; as a pre-anesthetic agent, 0.2 Gm. to 0.3 Gm. one-half to one hour before the patient is sent to the operating room

ELI LILLY AND COMPANY

Seconal Sodium (Powder) Bulk

Elixir Seconal Sodium Each 100 cc contains approximately 0.44 Gm of the barbiturate in a vehicle containing alcohol glycerin water and aromatics methenamine is present for the purpose of increasing the solubility of the barbiturate

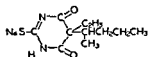
Pulvules Seconal Sodium 50 mg and 0.1 Gm

Suppositories Seconal Sodium 0.13 Gm. and 0.2 Gm

Seconal Sodium (Sterile Powder) 0.25 Gm and 0.5 Gm.
Dry powder used to prepare a 5 per cent solution by the addition of 5 cc. or 10 cc. respectively of sterile distilled water

U S patent 1 954 429 (April 10 1934 exp res 1951) U S trademark 328 662

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For descriptions and standards see the U S Pharmacopeia under Thiopental Sodium and Thiopental Sodium

marked by mental depression lasting for a few hours. It may be emphasized that the intravenous use of barbiturates may be a valuable procedure but such use is potentially dangerous and

lems involving respiratory depression laryngospasm and carbon dioxide oxygen balance. Atropine should be administered as premedication.

Dosage—Two or three cc. of a 2½ per cent solution is injected in about ten or fifteen seconds. The injection is then stopped to permit the complete effect to appear which requires from thirty to thirty five seconds. If relaxation has not occurred an additional 2 or 3 cc. may be injected at the same rate as before.

Caution: Aqueous solutions of thiopental sodium are not stable but decompose on standing; on boiling, a precipitation occurs.

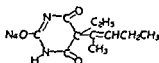
ABBOTT LABORATORIES

Pentothal Sodium: 0.5 Gm. and 1.0 Gm. ampuls. Buffered with anhydrous sodium carbonate, 30 mg. and 60 mg., respectively 5.0 Gm. multiple dose ampul. Buffered with anhydrous sodium carbonate 0.3 Gm.

Pentothal Sodium (Rectal): 3 Gm. vials. Buffered with anhydrous sodium carbonate 0.18 Gm.

U. S. patent 2,153,729 (April 11, 1939, expires 1956); U. S. patent 2,153,731 (April 11, 1939). U. S. trademark 334,340

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For tests and standards, see Section B.

Actions and Uses.—The actions and uses of vinbarbital sodium are similar to those for the intermediate-acting group of barbituric acid derivatives. It has a short induction period and a moderate duration of action. It is used for general sedation and hypnosis, pre-operative sedation, pre-anesthetic hypnosis, obstetrical sedation and amnesia. Its use occasionally gives rise to side effects such as epigastric discomfort, nausea, dizziness, pallor and even fall in blood pressure.

Dosage.—As a sedative, 32 mg. repeated three to four times daily; as a sedative and hypnotic, 0.1 Gm. to 0.2 Gm.; as a preoperative hypnotic 0.1 Gm. to 0.4 Gm.; to 0.4 Gm. with or given correspondingly.

Caution: Unbuffered aqueous solutions of vinbarbital sodium are not stable. The powder is hygroscopic, and if capsules are broken or exposed to high humidity the contents are affected by both moisture and carbon dioxide.

SHARP & DOHME, INC.

Capsules Delvinal Sodium: 0.1 Gm., 0.2 Gm. and 32 mg.

Elixir Delvinal Sodium: 473 cc. bottles. Each 30 cc. contains vinbarbital sodium 0.26 Gm. in a palatable elixir containing alcohol 33 per cent.

Solution Delvinal Sodium: 5 cc. ampuls and 20 cc. vials. Each cc. contains vinbarbital sodium 65 mg. in aqueous, 90 per cent propylene glycol solution.

Serums and Vaccines

of these potent and, in some cases, dangerous products has been partly met by a federal law entitled "An act to regulate the sale of viruses, serums, toxins and analogous products in the

It is to be noted that the protection of the federal law is of avail only in the case of prophylactic and therapeutic preparations which are imported or shipped for exportation or interstate sale. Only products which are licensed under the law referred to and which have not been found to conflict with the

serums

Official potency standards have been established or official potency tests are made at the National Institute of Health prior to the release of each lot for the following products: botulinus antitoxin, diphtheria antitoxin, *C. histolyticum* antitoxin, *C. oedematiens* antitoxin, staphylococcus antitoxin, tetanus antitoxin, scarlet fever streptococcus antitoxin, *perfringens* antitoxin, vibron, septique antitoxin, diphtheria toxin antitoxin mixture,

diphtheria toxoids, tetanus toxoids, antidysenteric serum, anti-meningococcic serum, type specific antipneumococcic serums, bacterial vaccines prepared from the typhoid bacillus, diphtheria toxin for the Schick test and scarlet fever streptococcus toxin for the Dick test and for immunization. For these products the dating of each lot is based on the last test for potency, that is, the date of manufacture is taken as the last date of satisfactorily passing a potency test. For all other biologic products, the testing for potency is on a less satisfactory basis, and the date of manufacture is counted as the date of removal from the animal in case of animal products, or the date of cessation of growth in the case of other products. For the purpose of determining the expiration date, the date of issue may be used instead of the date of manufacture, provided the product has been kept

Added Preservatives.—The safeguarding of serums, vaccines, etc., against bacterial contamination usually requires the addition of some antiseptic. The most commonly used antiseptics are cresol (0.4 per cent), phenol (0.5 per cent), glycerin, and organic mercury compounds.

Untoward Effects.—The use of serums and serum preparations is sometimes followed by certain untoward manifestations. These are due usually to sensitivity of the individual to animal products especially horse serum and in certain cases may be avoided by the use of serums which have been altered by the action of enzymes or by using serums from the bovine species or from sheep or goats. Serums and antitoxins, unless made by the inoculation of the horse, must show on the label the species of animal used.

SERUMS

IMMUNE SERUMS

Antitoxic serums

Antitoxins

Antivenin (Crotalus)
 Antivenin (Iatrodictus mactans)
 Botulism antitoxin
 Diphtheria antitoxin U S P
 Bivalent gas gangrene antitoxin U S P

Staphylococcus antitoxin
 Tetanus antitoxin U S P

Antibacterial serums

Antierysipeloid serum

NATURALLY PRODUCED ANTIBODIES

U S P F

VACCINES

Active immunization, General considerations

ATTENUATED LIVING VIRUSES OR KILLED VIRUSES

U S P

BACTERIAL TOXINS

Scarlet fever streptococcus toxin U S P
 Scarlet fever streptococcus toxin, tannic acid precipitated

BACTERIAL TOXINS, MODIFIED

Staphylococcus toxoid
 Tetanus toxoid U S P
 Tetanus toxoid, alum precipitated U S P
 S P
 precipitated U S P.

BACTERIAL VACCINES

Brucella vaccine
 Cholera vaccine U. S P

with diphtheria

Pertussis vaccine combined with diphtheria toxoid
 Pertussis vaccine combined with diphtheria and tetanus toxoids
 Pertussis Vaccine Combined with Tetanus Toxoid
 Plague vaccine-U. S. P.
 Smallpox vaccine
 Staphylococcus vaccine
 Rocky Mountain Spotted Fever Vaccine
 Typhoid vaccine-U. S. P.

TOXOID-VACCINE MIXTURES

Staphylococcus toxoid-vaccine mixture

DIAGNOSTIC AGENTS

Diphtheria toxin, diagnostic-U. S. P.
 Scarlet fever streptococcus toxin for Dick test
 Scarlet fever streptococcus antitoxin for Schultz-Charlton test
 Tuberculin

The following is a description of tuberculin U. S. P.

SERUMS

Normal Serums or Normal Blood Derivatives

This section lists those preparations derived from normal blood, such as plasma, serum or globulins. Any antibodies which the preparations may contain have been produced naturally in the body. There is definite evidence that human serum preparations may by carrying a virus, be instrumental in leading to the development of a form of infectious jaundice. They may also lead to reactions of the type usually regarded as allergic.

BLOOD GROUP SPECIFIC SUBSTANCES A AND B.—A sterile solution of polysaccharide-amino-acid complexes, capable of reducing the titer of the anti-A and anti-B isoagglutinins of group O donor blood. Blood group specific sub-

gastric mucosa.

Specific substances A and B, for trans-
 this elimi-
 agglutinins,
 nates reaction attributable to ...
 it should be kept in mind that group O blood may continue to

give rise to reactions due to pyrogens Rh incompatibility and immunologic unknowns

Dosage—Blood Group Specific Substances A and B may be added to group O blood just prior to administration or at the time of collection and storage One transfusion unit (10 cc.) is capable of reducing the anti B and anti B isoagglutinin titer of 500 cc of group O blood to at least one fourth of its original titer

SHARP & DOHME, INC.

Solution Blood Group Specific Substances A and B 10 cc. vials Preserved with phenol 0.3 per cent.

U S patent reissue No 22208 (Exp rat on Date July 14 1959)

HUMAN IMMUNE GLOBULIN U S P—Measles Prophylactic—Placental Extract.—A sterile solution of antibodies obtained from the placental blood and the placentae expelled by healthy women (*Homo sapiens*) Each preparation shall be composed of a pool from at least ten individuals Human immune globulin complies with the requirements of the National Institute of Health of the United States Public Health Service
U S P

For description and standards see the U S Pharmacopeia under Globulin Human Immune.

Actions and Uses—Human immune globulin is useful in the prevention and modification of measles It is equivalent in usefulness to convalescent serum but has the advantage of universal availability It has the disadvantage of producing reactions not always mild Most reactions however, can be avoided by the administration of the proper dosage which is necessarily modified in accordance with the stage of the incubation period or the prodromal stage of the disease. It is useful in the prevention of measles in institutional cases in larger doses than those given for modification. Prevention is of course less desirable than modification except where younger children ill with other diseases are apt to contract measles by exposure to a modified case Otherwise it is more desirable to permit a child to have

have led to refinement and concentration of the product and even to its oral administration the latter cannot be advocated on the basis of the evidence which is available at present

Dosage—The amount of human immune globulin which should be injected in a given case depends on the following factors

- 1 Whether modification or prevention is desired.
- 2 The age and general condition of the patient.
- 3 The intimacy of exposure

Careful consideration of the available literature is necessary to evaluate properly these factors and determine an entirely

satisfactory dosage, and even then it is not always possible to be certain of not obtaining prevention when modification is desired and vice versa. The following doses are recommended merely as a general pattern and are subject to adjustment in accordance with the factors listed above: for prevention, 2 to 10 cc.; for modification, 2 to 5 cc.

LEDERLE LABORATORIES, DIVISION AMERICAN CYANAMID Co.

Immune Serum Globulin (Human): 2 cc. and 10 cc. vials. Preserved with phenol 0.5 per cent.

Immune Serum Globulin (Human): 2 cc. vials. Preserved with sodium ethylmercurithiosalicylate, 1:10,000.

SHARP & DOHME, INC.

Immune Serum Globulin (Human): 2 cc. and 10 cc. vials. Preserved with phenol 0.5 per cent.

WYETH, INCORPORATED

Immune Serum Globulin (Human): 2 cc. and 10 cc. vials. Preserved with phenol 0.1 per cent and sodium ethylmercurithiosalicylate 0.01 per cent.

HUMAN SERUM IMMUNE GLOBULIN.—The gamma globulin fraction of normal adult human plasma. The finished product contains 16.5% of gamma globulin and complies with the minimum requirements of the National Institute of Health and as prepared by an acceptable method.

Actions and Uses.—For modification or complete protection against measles.

Dosage.—The volume of the dose per pound of body weight is 0.02-0.025 cc. for modification and at least 0.1 cc. for prevention when the product contains 150 mg of gamma globulin per cc.

CUTLER LABORATORIES

Immune Serum Globulin (Human): 2 cc vials. Preserved with sodium ethylmercurithiosalicylate 1:10,000.

Licensed by Research Corporation U. S. patent No. 2,390,074

CITRATED NORMAL HUMAN PLASMA-U. S. P.—

... whole blood from eight or more humans (Linné) who have been certified by a qualified doctor of medicine as free from any disease which is transmissible by blood

... tions into individual ... 50 cc. of a sterile, 4 per cent solution of sodium citrate in isotonic solution of sodium chloride for each 500 cc. of whole

blood The cell free plasma is separated by centrifugation, and transferred to a pool by means of a closed system Sterility tests are made, a preservative is added and the plasma is distributed into final containers through a closed system Citrated normal human plasma complies with the requirements of the National Institute of Health of the United States Public Health Service

"Citrated normal human plasma may be dispensed as liquid plasma, as frozen plasma, or as dried plasma Citrated normal human plasma must be free from harmful substances detectable by animal inoculation, and must not contain an excessive amount of preservative" U S P

For description and standards see the U S Pharmacopeia under Plasma, Citrated Normal Human

Actions and Uses—Citrated normal human plasma is administered in the treatment of surgical and traumatic shock, in the treatment of burns when loss of available plasma occurs, to combat hypoproteinemia, and as a temporary substitute for whole blood in the treatment of hemorrhage when whole blood is not immediately available Plasma and serum may be considered satisfactory substitutes for whole blood *except in those cases in which the administration of red blood corpuscles is regarded as essential*

Dosage—Citrated normal human plasma, whole or restored, is administered intravenously in amounts equivalent to those employed in the transfusion of whole blood but it should be remembered that plasma represents approximately one half the total volume of whole blood Average dose is 500 cc intravenously (U S P)

CUTTER LABORATORIES

Normal Human Plasma 300 cc bottles Preserved with sodium ethylmercurithiosalicylate 1 10 000

SAMUEL DEUTSCH SERUM CENTER, MICHAEL REESE RESEARCH FOUNDATION

Normal Human Plasma (Citrated) 60 cc. and 300 cc. bottles Contains dextrose in final concentration of 5 per cent

HYLAND LABORATORIES

Normal Human Plasma (Dried)• 50 cc. and 500 cc. bottles Containing an amount (preserved with phenylmercuric borate 1 15 000)

Normal Human Plasma (Citrated)• 300 cc. bottle containing dextrose 5 per cent Preserved with phenylmercuric borate 1 15 000

NORMAL HUMAN SERUM-U S P—The sterile serum obtained by pooling approximately equal amounts of the

is used to neutralize the venom injected by the bite inflicted by members of the crotalus family.

Dosage.—The serum is administered intramuscularly or subcutaneously; in cases seen late or in the presence of severe symptoms it may be administered intravenously. Certain observations seem to show serum in the vicinity should be allowed to incisions and suction. amount as is likely to prove beneficial.

ANTIVENIN (LATRODECTUS MACTANS). — An antitoxic serum prepared by immunizing horses against the venom of the black widow spider (*Latrodectus mactans*).

Actions and Uses.—This material, which is standardized on the basis of its ability to neutralize the venom of the black widow spider when the two are injected simultaneously in mice, is claimed to be indicated in the treatment of patients suffering from symptoms due to bites inflicted by the black widow spider (*Latrodectus mactans*). Prior to use, tests for serum sensitivity should be made, test material consisting of 1:10 dilution of isotonic solution of normal equine serum, which is injected intradermally. If there is a positive skin reaction, an eye test consisting of placing a few drops of the test material on the conjunctiva and watching for ten minutes should be undertaken. If there is a negative result from the skin test, the therapeutic serum can be administered. However, if there is a positive reaction in the eye following the positive skin test, serum therapy should be avoided. If there is a positive skin test and a negative eye test, the individual may be desensitized before administering the serum. The amount of material injected into the skin for the intradermal test should be not more than 0.02 cc. of the test material. The result can be evaluated in ten minutes, a positive reaction consisting of an urticarial wheal surrounded by a zone of erythema.

Associated treatment includes hot plunge baths, intravenous injection of magnesium sulfate, 20 cc of 10 per cent solution, or intravenous injection of 10 per cent calcium gluconate. Barbiturates may be used for restlessness. Apparently nothing is gained by local treatment at the site of the bite.

Dosage.—An injection of 2.5 cc of serum is administered intramuscularly.

SHARP & DOHME, INC.

Lyovac Antivenin (*Latrodectus mactans*): 'Vacule' vial containing a sufficient amount of lyophilized antivenin to yield 2.5 cc. of restored double-concentrated antivenin with phenol 0.35 per cent as a preservative; packaged with a 2.5 cc. vial of distilled water and one 1 cc. vial of normal horse serum (diluted 1:10) as test and desensitizing material.

A lyophilized antitoxic serum prepared by injecting horses with venom of black widow spiders (*Latrodectus mactans*).

A process of lyophilization consists in the following. The antivenin in specially designed final containers is immersed in a freezing mixture to congeal the substance rapidly with the least molecular rearrangement. The container is then subjected to a high vacuum to accomplish dehydration, which is continued until the residual moisture content is less than 1 per cent, and finally sealed under vacuum.

BOTULISM ANTITOXIN—An antitoxic serum prepared by immunizing animals against the toxins of two types of *Clostridium botulinum*

Actions and Uses—For prophylaxis and treatment of botulism. The clinical value of the antitoxin is uncertain

Dosage—Prophylactic subcutaneous injections of not less than 2,500 units of bivalent antitoxin. Therapeutic intravenous injection of not less than 10 000 units of the bivalent antitoxin to be repeated as indicated by the nature of the case.

DIPHTHERIA ANTITOXIN-U S P—"A sterile aqueous solution of antitoxic substances obtained from the blood serum or plasma of a healthy animal which has been immunized against diphtheria toxin. Diphtheria Antitoxin has a potency of not less than 500 antitoxic units per cc. It complies with the requirements of the National Institute of Health of the United States Public Health Service" *U S P*

For description and regulations see the *U S Pharmacopeia* under Diphtheria Antitoxin

Actions and Uses—For prophylaxis and treatment of diphtheria

Dosage—"Parenteral, therapeutic, 20 000 units, prophylactic, 1,000 units" *U S P*

BIVALENT GAS GANGRENE ANTITOXIN-U. S. P.

"A sterile solution of . . . blood of healthy animal"

Clostridium perfringens
package of Bivalent Gas
less than 10 000 antitoxic
toxins Bivalent Gas G
requirements of the Nat
States Public Health Service." *U S P*

For description and regulations see the *U S Pharmacopeia* under Gas Gangrene Antitoxin, Bivalent

ga . . . gas

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preferably the latter, repeated every twelve to twenty four hours depending on the symptoms in the individual case.

CUTLER LABORATORIES

Gas Gangrene Antitoxin 10 000 unit vials each of *Cl per*

fringens and *Cl. septicum* antitoxins. Preserved with tricresol 0.35 per cent.

ELI LILLY AND COMPANY

Gas Gangrene Antitoxin Concentrated (Combined):
10,000 unit vials each of *Cl. perfringens* and *Cl. septicum* anti-
toxins.

PENTAVALENT GAS GANGRENE ANTITOXIN.

U. S. P.—“A sterile solution of antitoxic substances obtained from the blood of healthy animals which have been immunized against the toxins of *Clostridium perfringens*, *Clostridium septicum*, *Clostridium oedematiens* (Novyi), *Clostridium bifermentans* (Kageless), *Clostridium colyt-*

For description and regulations see the U. S. under Gas Gangrene Antitoxin, Pentavalent.

Actions and Uses.—Used in prevention and gangrene. The clinical value of this

Dosage.—The minimum therapeutic dose

of *Cl. perfringens* and *Cl. septicum* :

1,500 units each of *Cl. novyi* and *Cl.*

3,000 units of *Cl. histolyticum*

to four times this dose may be given :

by additional injections in one to four
cated by the symptoms.

LEDERLE LABORATORIES, DIVISION AML

Gas Gangrene Antitoxin (valent): 10,000 unit vials each of *C. septicæ* antitoxins, 1,500 units each of antitoxins, and 3,000 units of *C. histolyticæ* antitoxins, preserved with phenol 0.4 per cent.

TRIVALENT GAS

U. S. P.—"A sterile solution of
from the blood of healthy animals

requirements of the National Institutes of Health, U.S. States Public Health Service."

For description and regulations see the U S Pharmacopeia under Trivalent Gas Gangrene Antitoxin

Actions and Uses—Used in prevention and treatment of gas gangrene. The clinical value of this antitoxin is questionable.

by the symptoms.

NATIONAL DRUG COMPANY

Gas Gangrene Antitoxin Refined and Concentrated Globulin (Trivalent): 10,000 unit vials each of *Cl perfringens* and *Cl septicum* antitoxins, and 1,500 units of *Cl oedematis* (Novyi) antitoxin. Preserved with tricresol 0.4 per cent.

PARKE, DAVIS & COMPANY

Gas Gangrene Antitoxin Refined and Concentrated (Combined, Trivalent): 10,000 unit vials each of *Cl perfringens* and *Cl septicum* antitoxins, and 1,500 units of *Cl novyi* antitoxin. Preserved with phenol 0.5 per cent.

E. R. SQUIBB & SONS

WYETH, INCORPORATED

Gas Gangrene Antitoxin, Concentrated and Refined (Trivalent): 10,000 units, syringe and vials, each of *Cl perfringens* and *Cl septicum* antitoxins, and 1,500 units of *Cl novyi* antitoxin. Preserved with phenol 0.25 per cent and sodium ethylmercurithiosalicylate 0.005 per cent.

TETANUS AND GAS GANGRENE ANTITOXINS.

U. S. P.—“A sterile solution of antitoxic substances obtained from the blood of healthy animals which have been immunized against the toxins of *Clostridium tetani* and *Clostridium perfringens* and *Clostridium septicum*. Each package of the Antitoxins shall contain not less than 1,500 units of tetanus antitoxin and not less than 2,000 units of each of the other component antitoxins. Tetanus and Gas Gangrene Antitoxins comply with the requirements of the U. S. P. of Health of the

S Pharmacopeia

Actions and Uses—Used in prevention of gas gangrene. The clinical value of this antitoxin is questionable except as relates to the tetanus antitoxin present.

Dosage.—Prophylactic: 1,500 units of tetanus antitoxin and 2,000 units each of *Cl. perfringens* and *Cl. septicum* antitoxins by parenteral injection. This dose may be repeated at intervals of from five to seven days depending on the severity of the wound. Local infiltration of the wound may be advisable.

CUTTER LABORATORIES

Tetanus-Gas Gangrene Antitoxin: 1,500 units of tetanus antitoxin and 2,000 units each of *Cl. perfringens* and *Cl. septicum* antitoxins in syringe and vials. Preserved with tricresol 0.35 per cent.

LEDERLE LABORATORIES, DIVISION AMERICAN CYANAMID CO

Tetanus-Gas Gangrene Antitoxin (Globulin Modified): 1,500 units of tetanus antitoxin and 2,000 units each of *Cl. perfringens* and *Cl. septicum* antitoxins in vials. Preserved with phenol 0.4 per cent and phenylmercuric borate 1:20,000.

ELI LILLY AND COMPANY

Tetanus-Gas Gangrene Antitoxin (Combined): 1,500 units of tetanus antitoxin and 2,000 unit vials each of *Cl. perfringens* and *Cl. septicum* antitoxins.

NATIONAL DRUG COMPANY

Tetanus-Gas Gangrene Antitoxin (Trivalent), Refined and Concentrated Globulin: 1,500 units of tetanus antitoxin and 2,000 units each of *Cl. perfringens* and *Cl. septicum* antitoxins and 300 units of *Cl. oedematiens* (Novyi) antitoxin in syringe and vials. Preserved with tricresol 0.4 per cent.

PARKE, DAVIS & COMPANY

Tetanus-Gas Gangrene Antitoxin (Combined) Prophylactic Refined and Concentrated (Combined): 1,500 units of tetanus antitoxin and 2,000 units each of *Cl. perfringens* and *Cl. septicum* antitoxins, syringe and vials. Preserved with phenol 0.5 per cent.

PITMAN-MOORE COMPANY, DIVISION OF ALLIED LABORATORIES, INC.

Tetanus-Gas Gangrene Antitoxin (Combined) Pepsin Digestion Refined: 1,500 units of tetanus antitoxin and 2,000 units each of *Clostridium perfringens* and *Clostridium septicum* antitoxins in syringe and vials.

E. R. SQUIBB & SONS

Tetanus-Gas Gangrene Antitoxin: 1,500 units of tetanus antitoxin and 2,000 units each of *Perfringens* and *Vibrio septicum* antitoxins in vials. Preserved with sodium ethylmercurithiosalicylate 1:20,000 and phenol 0.25 per cent.

U. S. STANDARD PRODUCTS CO

Tetanus-Gas Gangrene Antitoxin, Refined and Concentrated: 1,500 units of tetanus antitoxin and 2,000 units each of

SERUMS AND VACCINES

Cl. perfringens and *Cl. septicum* antitoxins in syringe with cresol 0.4 per cent.

WYETH, INCORPORATED

Tetanus Gas Gangrene Antitoxin (Prophylactic and Concentrated) 1500 units of tetanus antitoxin each of *Cl. perfringens* and *Cl. septicum* antitoxin in syringe and vial and packaged with a 1 cc vial of (1:10) antitoxin for determination of sensitivity to horse serum. Preserved with phen 1.025 per cent and sodium ethylmercuriosalicylate 0.005 per cent.

SCARLET FEVER STREPTOCOCCUS ANTITOXIN—U. S. P.—Scarlet Fever Antitoxin.—A sterile solution of antitoxic substances obtained from the blood serum of a healthy animal which has been immunized against the toxin produced by the streptococcus regarded as causal of scarlet fever. Scarlet Fever Streptococcus Antitoxin has a potency of not less than 400 antitoxic units per cc. It complies with the requirements of the National Institute of Health and the United States Public Health Service U. S. P. For description and standards see the U. S. Pharmacopeia under Scarlet Fever Streptococcus Antitoxin.

Actions and Uses.—There is satisfactory evidence that scarlet fever is caused by hemolytic streptococci and that the administration of a serum containing the antitoxin produced by these organisms favorably influences the course of scarlet fever. It is also believed that temporary immunity against scarlet fever may be established through the use of such a serum but the prophylactic use generally is not considered advisable. The serum is also used to distinguish the rash of scarlet fever from other rashes by the production of a blanched area at the site of its intradermal injection.

Dosage.—Prophylactic 3000 U. S. P. H. S. units therapeutically 9000 U. S. P. H. S. units

PARKE, DAVIS & COMPANY

Scarlet Fever Streptococcus Antitoxin 3000 and 9000 unit vials

STAPHYLOCOCCUS ANTITOXIN.—Antitoxin prepared by immunizing horses with staphylococcus toxoid and/or staphylococcus toxin. The antitoxin is standardized on the basis of the international unit which was adopted by the Permanent Commission on Biological Standardization of the Health Organization of the League of Nations in 1934 the unit being the equivalent to approximately 125 original antidermonecrotic units an antidermonecrotic unit being that amount of antitoxin required to neutralize one necrotizing dose of staphylococcus toxin.

Actions and Uses.—Staphylococcus antitoxin is suggested in

the treatment of acute and severe staphylococcic infections with or without septicemia. Its use in treatment calls for adequate dosage administered early; most of the antitoxin estimated to be necessary for the entire treatment of the infection should be

a part of the treatment. Probably chemotherapeutic preparations should take precedence over this antitoxin in routine treatment.

Dosage.—For the treatment of localized infections, 10,000

temperature have subsided and the blood cultures are sterile for three consecutive days.

TETANUS ANTITOXIN—U. S. P.—Purified Antitetanic Serum.—Concentrated Tetanus Antitoxin.—Refined Tetanus Antitoxin.—Antitetanic Globulins.—“Tetanus Antitoxin is a sterile aqueous solution of antitoxic substances obtained from the blood serum or plasma of a healthy animal which has been immunized against tetanus toxin. Tetanus antitoxin has a potency of not less than 400 antitoxic units per cc. It complies with the requirements of the National Institute of Health of the U. S. P.”

For U. S. Pharmacopeia under

Actions and Uses.—Tetanus antitoxin is highly effective in the prevention of tetanus, but its effectiveness when used in the treatment of the disease is much less certain.

Dosage.—By parenteral injection: therapeutic, 20,000 units; prophylactic, 1,500-3,000 units or more; both to be repeated at short intervals as indicated. Intrathecal administration generally is regarded as inadvisable.

ANTIBACTERIAL SERUMS

More complex in action than the antitoxins and in general less satisfactory for therapeutic purposes are those antibodies which resist the bacteria themselves. They are believed to act primarily by combining chemically with antigens on the bacterial surfaces, thereby rendering the bacteria susceptible to phagocytosis by polymorphonuclear and mononuclear leukocytes. The sphere of usefulness of the antibacterial sera is open to much discussion, and is in need of constant reevaluation in particular with the progress of chemotherapy.

ANTI-ERYSIPELOID SERUM.—A serum containing the antibodies and antibacterial properties for *Erysipelothrix rhusiopathiae* (suis). The serum is prepared from horses subjected to increasing subcutaneous injections of live cultures of

the organism Potency is tested on pigeons in which 0.1 cc. of the serum protects against infection lethal to controls in from three to four days

Actions and Uses—For treatment of the clinical condition known as erysipeloid which is not to be confused with erysipelas

Dosage—It is suggested that from 10 to 20 cc be administered subcutaneously or intramuscularly and quantities of 0.25 to 0.5 cc. at numerous places about the border of the lesion

PITMAN MOORE COMPANY DIVISION OF ALLIED LABORATORIES, INC.

Anti Erysipeloid Serum (Refined) 10 cc vial Preserved with sodium ethylmercurithiosalicylate 1:10,000

Naturally Produced Antibodies

In certain infectious diseases the etiological agent may be of such a nature as to make it impractical to produce a satisfactory immune serum in animals In the absence of artificially

of antibodies however is not as great as when animals are artificially immunized by the repeated injection of antigens An outstanding attribute of naturally produced antibodies or convalescent serums is that their source is from a member of the same species and thus there is less danger of a reaction to the protein of another species but reaction may occur even with human serums Even human serum, however should be used only where there is definite need since infectious jaundice has been transmitted through the serum

HUMAN MEASLES IMMUNE SERUM N. F.—Measles Convalescent Serum—Human Measles Immune Serum is sterile serum obtained from the bloods of healthy humans (*Homo sapiens*)

It complies with the requirements of the Health of the United States

For description and standardization see under Human Measles Immune Serum

Actions and Uses—Human measles immune serum is administered during the incubation period to prevent or modify the expected attack of measles

Dosage—To prevent the disease in infants and children of 6 years or under 10 cc is given intramuscularly within five days after exposure For children between 7 and 12 years of age, 15 cc. is given and for older children and adults 20 cc is given in like manner

Whether the serum is given for prevention or modification depends on the number of days the patient has been exposed

If prevention is desired, however, the dosage may have to be increased corresponding to the increase in days after exposure of the patient. If injection is made on the sixth or seventh day after exposure, a high percentage of patients have a modified type of measles which is followed by lasting immunity. It is probable that serum given after the seventh day following the initial exposure has little effect in either preventing or modifying the disease.

The serum may be given either intravenously or intramuscularly. Vacuum dried serum should be given only intramuscularly.

MILWAUKEE CONVALESCENT SERUM CENTER

Measles Immune Serum (Human): 5 cc. and 7.5 cc. vials.
Preserved with sodium ethylmercurithiosalicylate 1:10,000.

SAMUEL DEUTSCH SERUM CENTER, MICHAEL REESE RESEARCH
FOUNDATION

Human Convalescent Measles Serum: 5 cc., 7.5 cc. and 20 cc. vials. Preserved with phenylmercuric borate 1:15,000.

HUMAN SCARLET FEVER IMMUNE SERUM.

N. F. C. "Human Scarlet Fever Amongst Seamen." "Human Scarlet Fever of heal of sea Nation Service." N. F.

For description and regulations see The National Formulary under Serum Human Scarlet Fever Immune.

Actions and Uses—Human scarlet fever immune serum is of value in transferring passive immunity to a patient exposed to scarlet fever. The evidence as to therapeutic activity is conflicting. It may be used in patients sensitive to horse serum, though the antitoxic content of convalescent serum is low. It does not seem wholly adequate to meet septic complications.

Dosage.—For prophylaxis in infants and young children under 6 years of age, 10 cc. is given; for children between 6 and 12 years of age, 15 cc., and over 12 years of age and for adults 15 to 20 cc. is given, intramuscularly. If the individual is continuously exposed, it is recommended that a second dose be given ten days after the first injection.

MILWAUKEE CONVALESCENT SERUM CENTER

Scarlet Fever Immune Serum (Human): 10 cc. and 20 cc. vials. Preserved with sodium ethylmercurithiosalicylate 1:10,000.

SAMUEL DEUTSCH SERUM CENTER, MICHAEL REESE RESEARCH
FOUNDATION

Human Convalescent Scarlet Fever Serum: 10 cc. and 20 cc. vials. Preserved with phenylmercuric borate 1:15,000.

HUMAN SERUM IMMUNE GLOBULIN — The gamma globulin fraction of normal adult human plasma. The finished product contains 16.5 per cent of gamma globulin and complies with the minimum requirements of the National Institute of Health and as prepared by an acceptable method.

Actions and Uses—For modification or complete protection against measles.

Dosage—The volume of the dose per pound or body weight is 0.02–0.025 cc. for modification and at least 0.1 cc. for prevention when the product contains 150 mg. of gamma globulin per cc.

CUTTER LABORATORIES

Immune Serum Globulin (Human) 2 cc. vials Preserved with sodium ethylmercurithiosalicylate 1:10,000

Licensed by Research Corporation U. S. patent 2,390,074

PERTUSSIS IMMUNE SERUM (HUMAN)—The sterile serum prepared from the pooled blood of healthy adult human beings who have had whooping cough in childhood and who have received repeated courses of Phase I Pertussis Vaccine. The bloods from which pooled plasma is to be prepared and processed are drawn about 1 month after a course or courses of vaccine, when the donor serum agglutination titer has become greatly elevated, usually 1:640 or higher. The serum

dried may be administered intravenously or intramuscularly for prophylaxis and treatment of whooping cough. The refined and concentrated product must not be administered intravenously but is intended for both prophylactic and therapeutic use.

Dosage—For treatment, three 20 cc. doses at forty-eight hour intervals may be injected. A fourth dose may be necessary. Critically ill infants may be given from 60 cc. to 100 cc. intravenously repeated one or more times.

The foregoing dosage applies only to the unmodified serum. The refined and concentrated serum is several times more potent than the unmodified product. Follow the dosage recommended on the package label.

CUTTER LABORATORIES

Antisera Serum (Human) A light colored serum

the condition of the patient

HYLAND LABORATORIES

Pertussis Immune Serum (Human) Vacuum-dried powder, representing 20 cc. vials Preserved with sodium ethylmer-

THE NATIONAL DRUG CO.

Influenza Virus Vaccine, Types A and B: Packages of 1 cc. and 5 cc. vials. Preserved with sodium ethylmercurithiosalicylate .01 per cent.

PITMAN-MOORE COMPANY, DIVISION OF ALLIED LABORATORIES,
INC.

Influenza Virus Vaccine, Types A and B, Refined and Concentrated: Packages of one vial, 5 cc. (five doses). Preserved with sodium ethylmercurithiosalicylate 1:10,000.

SHARP & DOHME, INC.

Influenza Virus Vaccine, Types A and B, Protamine Concentrated and Refined: Packages of twenty-five, 1 cc. and 5 cc. vials. Preserved with sodium ethylmercurithiosalicylate 1:10,000.

E. R. SQUINN & SONS

Influenza Virus Vaccine, Types A and B, Refined and Concentrated: Packages of 1 cc. and 10 cc. vials. Preserved with sodium ethylmercurithiosalicylate 1:10,000.

RABIES VACCINE.—U. S. P.—"An uncontaminated suspension of the attenuated, diluted, dried or dead, fixed virus of rabies. The virus is obtained from the tissue of the central nervous system of an animal suffering from fixed virus rabies infection. Rabies Vaccine complies with the requirements of the National Institute of Health of the United States Public Health Service." *U. S. P.*

For description and standards see the U. S. Pharmacopeia under Rabies Vaccine.

Actions and Uses.—By treatment with rabies vaccine after the bite of a rabid animal, immunity is often established before the incubation period of the disease is completed, and rabies is thus prevented. The treatment fails not infrequently, and in a small percentage of cases it is followed by paralysis, which is usually transient but rarely may be permanent or even fatal.

BAY'S VACCINE (CHUMING) : The vaccine is

Actions, Uses and Dosage.—When employed for the treatment of rabies, the treatment is divided into two classes: mild, requiring 14 doses; severe, requiring 21 doses. One dose, 2 cc., is given daily over a period of either 14 or 21 days.

RABIES VACCINE (HARRIS).—Brains and spinal cords of rabbits killed after complete paralysis, following infection with fixed virus, are ground to a paste, frozen with carbon

dioxide snow, and rapidly dried *in vacuo*. The resulting dry powder is standardized by the method devised by Dr. Harris and stored *in vacuo* in the cold. One dose is given daily over a period of 10 days or more, doses increasing in unitage up to a maximum.

DR. D. L. HARRIS LABORATORY

Rabies Vaccine (Harris): Vacuum sealed tubes packaged in series of ten consecutive doses of increasing potency, with ten vials of physiological solution of sodium chloride to prepare the vaccine suspension, and a Luer syringe with needle.

ELI LILLY AND COMPANY

Rabies Vaccine (Harris): 0.5 cc vials, packaged in series of fourteen doses, with a special syringe unit.

RABIES VACCINE (PASTEUR) — (PASTEUR ANTIRABIC VACCINE)

Dosage—Prophylactic treatment consists of twenty one doses which are administered at twenty four hour intervals and these are sent in three installments of seven doses each. The installments are sent by special delivery mail. The first dose consists of two sections of a cord dried for six days, the second dose consists of two sections of a cord dried for five days, and the third dose two sections of a cord dried for four days. The remaining eighteen doses are prepared from single sections of cords dried as follows: 3, 3, 2, 2, 1, 5, 4, 4, 3, 3, 2, 2, 4, 3, 2, 3, 2, 1 days. They are administered in the order listed. Each dose of the dried cord is diluted with 2.5 cc of sterile sodium chloride solution in the syringe at the time of injection.

RABIES VACCINE (SEMPLE)—An antirabic vaccine prepared according to the general method of David Semple (phenol killed). The brains or brains and spinal cords of rabbits killed on about the sixth day after inoculation with the fixed virus of rabies are triturated with isotonic solution of sodium chloride containing 1 per cent phenol. Various concentrations of nerve tissue are employed. The mixture is strained, incubated at 37 C for (usually) 24 hours and then diluted with an equal volume of isotonic solution of sodium chloride, so that the finished product contains a definite amount of brain substance and about 0.5 per cent phenol. Put up in containers, each containing usually, sufficient material for a daily dose.

Actions and Uses—Rabies vaccine (Semple) is used in the prophylactic treatment of rabies.

Dosage—0.5 cc., 1 cc., 2 cc. or 3 cc. of the suspended vaccine

(depending on the dilution employed) daily over a period of it is supplied.

LEDERLE LABORATORIES, DIVISION AMERICAN CYANAMID CO

Rabies Vaccine (Semple Method): 2 cc. vials packaged in units of seven vials. Preserved with phenol 0.25 per cent and sodium ethylmercurithiosalicylate 1:20,000.

NATIONAL DRUG COMPANY

Rabies Vaccine (Phenol Killed): 0.5 cc. vials in packages of seven, without syringe, and packages of fourteen with syringe. Preserved with phenol 0.25 per cent and sodium ethylmercurithiosalicylate 1:10,000.

SHARP & DOHME, INC.

Rabies Vaccine (Phenol Killed): 0.5 cc. vials containing a 20 per cent brain tissue suspension packaged in units of seven vials without syringe, and a single Rabies Vaccine Syringe.

U. S. STANDARD PRODUCTS CO.

Rabies Vaccine (Semple Method): 0.5 cc. vials packaged in units of seven and fourteen vials; 1 cc. vials packaged in units of fourteen vials; 2 cc. vials and 2 cc. syringes each packaged in units of seven and fourteen vials or syringes, and the latter in units of twenty-one syringes. Preserved with phenol 0.5 per cent.

WYETH, INCORPORATED

Rabies Vaccine (Semple Method): 2 cc. syringes each packaged in units of fourteen syringes. Preserved with phenol 0.5 per cent.

Rabies Vaccine (Modified Semple Method): 0.5 cc. vials packaged in units of seven vials. Preserved with phenol 0.5 per cent.

RABIES VACCINE PREPARED BY ULTRAVIOLET IRRADIATION

with fixed a desired sodium chloride solution containing sufficient material for a daily dose.

Actions and Uses.—Rabies vaccine (ultraviolet irradiation killed) is employed for the prophylaxis of rabies.

for 14 to
central
to seven

PITMAN MOORE COMPANY

Rabies Vaccine (Ultraviolet Irradiation Killed Virus)
 1 cc. vials packaged in units of seven vials of a 10 per cent suspension Preserved with sodium ethylmercurithiosalicylate
 1 10 000

E R SQUIBB & SONS

Rabies Vaccine (Ultraviolet Irradiation Killed Virus)
 2 cc. vials packaged in units of seven vials of a 5 per cent suspension Preserved with sodium ethylmercurithiosalicylate
 1 10 000

Bacterial Toxins

Bacterial toxins are sterile solutions obtained by filtering fluid cultures of the microorganisms through bacteria excluding filters. The filtrate of toxin contains in addition to the true bacterial toxin produced during the growth of the microorganisms metabolic products liberated by the microorganisms during their growth in the medium soluble components of the bacterial cells and the unused portions of the culture medium.

SCARLET FEVER STREPTOCOCCUS TOXIN
U S P—Dick Test Toxin—A sterile solution in a medium containing not more than 1 per cent of peptone but no meat extractive of certain products including a soluble toxin result

For diagnostic scarlet fever preparations see under Diagnostic Agents

Actions Uses and Dosage—The toxin is used for active immunization. For this purpose it is injected subcutaneously at weekly intervals. The amount of toxin necessary for immunity production varies with the individual. Five to six doses are given beginning with 162 to 650 skin test doses for the first injection and increasing the amount of toxin in each subsequent injection to a final dose of 100 000 to 120 000 skin test doses. Immunity to the toxin appears in a few weeks and is determined by the absence of a reaction to the intracutaneous test.

NATIONAL DRUG COMPANY

Scarlet Fever Streptococcus Toxin for Immunization
 1 cc. vials packaged in units of five vials containing respectively 650 2 500 10 000 30 000 and 100 000 120 000 skin test doses per cubic centimeter. 10 cc. vials packaged in units of five vials containing respectively 650 2 500 10 000 30 000 and 100 000 120 000 skin test doses per cubic centimeter. Preserved with 0.5 per cent phenol.

PARKE, DAVIS & COMPANY

Scarlet Fever Streptococcus Toxin for Immunization: 1 cc. and 10 cc. vials (one and ten immunizations, respectively), each packaged in units of five vials containing respectively 650, 2,500, 10,000, 30,000 and 100,000-120,000 skin test doses per cc. The 1 cc. vial, containing 100,000-120,000 skin test doses per cc., also packaged separately.

SHARP & DOHME, INC.

Scarlet Fever Streptococcus Toxin for Immunization: 1 cc. and 10 cc. vials (single and ten immunization doses respectively), each packaged in units of five vials containing, respectively, 650, 2,500, 10,000, 30,000 and 100,000-120,000 skin test doses per cubic centimeter; the 1 cc. vial containing 100,000-120,000 skin test doses is also packaged separately.

E. R. SQUIBB & SONS

Scarlet Fever Streptococcus Toxin for Immunization: 1 cc. vials packaged in units of five vials containing, respectively, 650, 2,500, 10,000, 30,000 and 100,000-120,000 skin test doses per cubic centimeter, 10 cc. vials packaged in units of five vials containing, respectively, 650, 2,500, 10,000, 30,000 and 100,000-120,000 skin test doses per cubic centimeter and in single vial packages containing 100,000-120,000 skin test doses. Preserved with phenol 0.5 per cent and buffered monobasic potassium phosphate and sodium hydroxide.

U. S. STANDARD PRODUCTS CO.

Scarlet Fever Streptococcus Toxin for Immunization: 1 cc. vials packaged in units of five vials containing, respectively, 650, 2,500, 10,000, 30,000 and 100,000-120,000 skin test doses per cubic centimeter; 10 cc. vials packaged in units of six vials containing, respectively, 650, 2,500, 10,000, 30,000, 100,000-120,000 and 100,000-120,000 skin test doses per cubic centimeter. Preserved with phenol 0.5 per cent.

SCARLET FEVER TANNIC ACID IN, red
 solution containing 1 of
 scarlet fever toxin. 0.4
 per cent phenol and complies with the requirements of the National Institute of Health of the United States Public Health Service

Actions and Uses—This tannic acid precipitated toxin is claimed to permit slower absorption and a prolonged antigenic stimulus which permits a reduction in the amount of toxin and size of dose as compared with former methods of immunization.

Dosage.—Children receive three intracutaneous injections of 0.1 cc. (dose 1, 750 STD/0.1 cc.; dose 2, 3,000 STD/0.1 cc.; dose 3, 10,000 STD/0.1 cc.) at two week intervals. Some may need a supplemental dose after a four week interval.

Adults may receive 500, 2,000, 6,000 and 10,000 STD at two week intervals. Each vial should be well shaken before use. The toxin should not be used beyond expiration date on label or if it does not resuspend completely on shaking.

WYETH, INCORPORATED

Scarlet Fever Streptococcus Toxin for Immunization, Tannic Acid Precipitated. 0.5 cc. single immunization vials and 2 cc. 10 immunization vials packaged in units of three vials (children) contains respectively in each 0.1 cc. 750, 3,000 and 10,000 skin test doses, and in units of four vials (adult) con-

Bacterial Toxins, Modified

Certain bacterial toxins may be modified so as to retain their capacity for bringing about an immune response while at the same time they are made relatively harmless, or at least their toxicity is greatly decreased. Examples of such modified bacterial toxins are Diphtheria Toxin Antitoxin Mixture and Diphtheria Toxoid.

TOXIN-ANTITOXIN MIXTURE

theria antitoxin

The product should be used only if clear and free from sediment or flocculi.

The antitoxin used in diphtheria toxin antitoxin mixture is produced from the horse, goat or sheep. Diphtheria toxin-antitoxin mixture has been largely supplanted by diphtheria toxoid.

Actions, Uses and Dosage—Diphtheria toxin antitoxin mixture is used for active immunization against diphtheria. It is employed chiefly for those who react severely to toxoid principally older children and adults, ordinarily diphtheria toxoid is preferred. It is administered at the insertion of the deltoid of one week between doses six months after the last her immunization is necessary. In the presence of an outbreak of diphtheria an immunizing dose of diphtheria antitoxin alone should be used if exposed children cannot be kept under regular medical observation.

TOXOIDS

DIPHTHERIA TOXOID.—U. S. P.—Anatoxin-Ramon.—

Diphtheria Anatoxin.—"A sterile solution of the products of *Corynebacterium diphtheriae* (theriae) . . . bility to . . . perty of . . . Toxoid . . . ie adult

human does not cause either local or general symptoms of diphtheria poisoning in a guinea pig within 30 days after its injection into the animal. The antigenic value shall be such that the initial dose for the human shall protect at least 80 per cent of guinea pigs, 6 weeks after injection, against five minimum lethal doses each of diphtheria test toxin. Diphtheria Toxoid complies with the requirements of the National Institute of Health of the United States Public Health Service." *U. S. P.*

For description and regulations see the *U. S. Pharmacopeia* under Diphtheria Toxoid.

Actions, Uses and Dosage.—Diphtheria toxoid is used for active immunization against diphtheria. It is administered subcutaneously, preferably at the insertion of the deltoid, in two or three doses of 1 cc. each with an interval of three or four weeks between doses. Since some local and general reactions have been observed in adults and in children over 8 years of . . . 0.1 cc. of the toxoid diluted . . . olution should be given to

CUTTER LABORATORIES

Diphtheria Toxoid: 1 cc. and 30 cc. vials in packages of three 1 cc. vials, and one 30 cc. vial. Preserved with sodium ethylmercurithiosalicylate 1:10,000.

LEDERLE LABORATORIES, DIVISION AMERICAN CYANAMID CO.

Diphtheria Toxoid: 1 cc. and 30 cc. vials in packages of three 1 cc. vials, and one 30 cc. vial. Each package is accompanied by a vial containing sufficient diluted diphtheria toxoid for ten sensitivity tests.

ELI LILLY AND COMPANY

Diphtheria Toxoid: 1 cc. and 30 cc. vials in packages of three 1 cc. vials, and one 30 cc. vial. Preserved with sodium ethylmercurithiosalicylate 1:10,000.

NATIONAL DRUG COMPANY

Diphtheria Toxoid: 3 cc. vials (one immunization) and 30 cc. vials. Preserved with sodium ethylmercurithiosalicylate 1:10,000.

PARK, DAVIS & COMPANY

Diphtheria Toxoid Plain. 1 cc. and 30 cc. vials in packages containing three 1 cc vials, and one 30 cc. vial

SHARP & DOHME, INC.

Diphtheria Toxoid. Vials of 3 cc. (1 three-dose immunization) and 30 cc (10 three dose immunizations)

E. R. SQUIBB & SONS

Diphtheria Toxoid: 30 cc. vial in single packages Preserved with sodium ethylmercurithiosalicylate 1 10,000

Diphtheria Toxoid for Reaction Test 1 cc vial containing sufficient for ten tests

U S STANDARD PRODUCTS CO

Diphtheria Toxoid. 1 cc., 60 cc., 20 cc. and 30 cc. vials in packages of two 1 cc. vials, one 6 cc. vial, one 20 cc. vial, and one 30 cc. vial

WYETH, INCORPORATED

Diphtheria Toxoid. 1 cc. and 30 cc. vials in packages of two and of twenty 1 cc. vials, and one 30 cc. vial Each package is accompanied by a sufficient amount of diluted diphtheria toxoid for the reaction test

DIPHTHERIA TOXOID, ALUM PRECIPITATED.

U. S. P.—“A sterile suspension of diphtheria toxoid precipitated with alum from the solution of the active principle of the diphtheria toxin.”

“It is a sterile suspension of the active principle of the diphtheria toxin, precipitated with alum, and is used for active immunization.”

“It is a sterile suspension of the active principle of the diphtheria toxin, precipitated with alum, and is used for active immunization.”

For description and regulations see the U S Pharmacopeia under Diphtheria Toxoid, Alum Precipitated

Actions, Uses and Dosage—Diphtheria toxoid alum precipitated, is used for active immunization.

It is administered subcutaneously or intramuscularly.

the diphtheria product, administered subcutaneously or intramuscularly for active immunization, 1 cc. or 0.5 cc. (which ever is specified on the label) to be repeated once with an interval of 4 to 6 weeks”

U S P

LEDERLE LABORATORIES, DIVISION AMERICAN CYANAMID CO

Refined Diphtheria Toxoid (Alum Precipitated) 0.5 cc., 1 cc and 5 cc. vials in packages of two 0.5 cc. vials, two 1 cc. vials one 5 cc. vial and one 10 cc vial Preserved with sodium ethylmercurithiosalicylate 1 10,000

DIPHTHERIA AND TETANUS TOXOIDS, ALUM PRECIPITATED-U. S. P.—"Alum Precipitated Diphtheria and Tetanus Toxoids is a turbid, white, slightly gray or slightly pink suspension prepared by mixing suitable quantities of alum precipitated diphtheria toxoid and alum precipitated tetanus toxoid, each of which possesses adequate potency to permit combining. The toxoids shall be mixed in such proportions that each cc., or less, of the combined toxoids will contain one individual human dose of each of the active ingredients. Alum Precipitated Diphtheria and Tetanus Toxoids complies with the requirements of the National Institute of Health of the United States Public Health Service" U S P

For regulations, see the U S Pharmacopeia under Diphtheria and Tetanus Toxoids, Alum Precipitated

Actions, Uses and Dosage—Diphtheria and Tetanus Toxoids, Alum Precipitated, is used for active immunization against diphtheria and tetanus. It is administered subcutaneously, preferably at the insertion of the deltoid muscle. Because of the physical character of the product absorption is delayed. The dosage is "Hypodermic, for active immunization 1 cc. to be repeated once with an interval of four to six weeks. Additional doses may be required to secure a negative Schick test." U S P

LEDERLE LABORATORIES DIVISION AMERICAN CYANAMID CO

Combined Diphtheria-Tetanus Toxoids (Alum Precipitated Refined) 1 cc. and 10 cc. vials in packages of two 1 cc. vials and of one 10 cc. vial

ELI LILLY AND COMPANY

Combined Diphtheria Toxoid-Tetanus Toxoid (Alum Precipitated) 1 cc. and 10 cc. vials in packages of two 1 cc. vials (one immunization) and of one 10 cc. vial (five immunizations)

NATIONAL DRUG COMPANY

Combined Diphtheria and Tetanus Toxoids (Alum Precipitated) Two 0.5 cc. vials (one immunization) and two 2.5 cc. vials (five immunizations) Dosage Two 0.5 cc. subcutaneous injections at four to six week intervals Preserved with sodium ethylmercurithiosalicylate 1:10,000

PARKE, DAVIS & COMPANY

Combined Diphtheria Tetanus Toxoid Packages of three 2 cc. vials and packages of one 30 cc. vial

Combined Diphtheria Tetanus Toxoid (Alum Precipitated) 1 cc. vial. Preserved with Phenol 1:20,000

PITMAN-MOORE COMPANY

Combined Diphtheria-Tetanus Toxoid (Alum Precipitated): Packages of two 1 cc. vials and packages of one 10 cc. vial. Preserved with sodium ethylmercurithiosalicylate 1:10,000.

SHARP & DOHME, INC.

Combined Diphtheria-Tetanus Toxoid (Alum Precipitated): 1 cc. and 10 cc. vials in packages of two 1 cc. vials and of one 10 cc. vial. Preserved with sodium ethylmercurithiosalicylate 1:10,000.

E. R. SQUIBB & SONS

Combined Diphtheria Toxoid-Tetanus Toxoid (Alum Precipitated): 1 cc. and 10 cc. vials in packages of two 1 cc. vials and of one 10 cc. vial.

WYETH, INCORPORATED

Combined Diphtheria-Tetanus Toxoid (Alum Precipitated): 1 cc. and 10 cc. vials in packages of two 1 cc. vials and of one 10 cc. vial.

STAPHYLOCOCCUS TOXOID.—*Staphylococcus* Anatoxin—Univalent or polyvalent, potently hemolytic and dermonecrotic toxins of *Staphylococcus aureus* and *albus* altered by the formaldehyde-detoxifying process of Burnett (modified from Ramon). Antigenicity is maintained but toxicity is greatly diminished. The antigenic potency is determined by injecting 1 cc. of toxoid per kilogram intravenously into three rabbits and the resulting serum tested at the end of one and two weeks for its content of staphylococcus antitoxin. No staphylococcus toxoid is used which in doses of 0.2 cc. or less of the undiluted material will cause necrosis when injected into rabbits. The toxin is titrated to determine its dermonecrotic potency.

Actions, Uses and Dosage.—*Staphylococcus* toxoid has been reported a valuable agent in the prophylaxis and therapy of various staphylococcic pyodermas and localized pyogenic processes due to *Staphylococcus aureus* and *albus* (boil, carbuncle, furunculosis, acne, and so on). The toxoid is said to be effective in producing active immunity to the dermonecrotic and hemolytic elements of the toxins of *Staphylococcus aureus* and *albus*, irrespective of the individual strain of the infecting organism. The toxoid induces the production of staphylococcus antitoxin in the blood serum of immunized persons.

The initial dose should be not more than 0.1 cc. containing 10 skin necrotizing doses, injected subcutaneously at the insertion of the deltoid. Subsequent doses at weekly intervals should be increased by 10 to 20 skin necrotizing doses. Marked local, or a systemic reaction to any dose contraindicates increase of the succeeding dose.

LEDERLE LABORATORIES, DIVISION AMERICAN CYANAMID CO

Staphylococcus Toxoid: Two 5 cc. vials, one containing

toxoid derived from 100 necrotizing doses of toxin and one containing toxoid derived from 1,000 necrotizing doses of toxin.

NATIONAL DRUG COMPANY

Staphylococcus Toxoid. Two 5 cc. vials, one containing 100 necrotizing doses and one containing 1,000 necrotizing doses of toxin

PARKE, DAVIS & COMPANY

Staphylococcus Toxoid. Two 5 cc. vials, one containing 100 necrotizing doses and one containing 1 000 necrotizing doses of toxin

PITMAN MOORE COMPANY, DIVISION OF ALLIED LABORATORIES, INC.

Staphylococcus Toxoid 5 cc vials containing in each cubic centimeter the toxoid derived from 1,000 necrotizing doses of toxin Preserved with sodium ethylmercurithiosalicylate 1 10 000

SHARP & DOHME, INC.

TETANUS TOXOID-U. S. P.—Tetanus Toxoid is a sterile solution of the product of growth of the tetanus bacillus

test toxin into each animal U. S. P.

For description and regulations see the U. S. Pharmacopoeia

CUTTER LABORATORIES

Tetanus Toxoid Packages of three 1 cc. vials and a 30 cc package Preserved with phenylmercuric nitrate 1 25 000

LEDERLE LABORATORIES, DIVISION AMERICAN CYANAMID CO.

Tetanus Toxoid (Fluid): 1 cc. and 30 cc. vials in packages of three 1 cc. vials and one 30 cc. vial.

TETANUS TOXOID, ALUM PRECIPITATED.

U. S. P.—"A sterile suspension of tetanus toxoid, precipitated with alum from a solution in which the products of growth of the tetanus bacillus (*Clostridium tetani*) have developed and have been so modified by special treatment as to have lost the ability to cause toxic effects in guinea pigs, but retaining the property of inducing active immunity.

"Alum Precipitated Tetanus Toxoid complies with the requirements of the National Institute of Health of the United States Public Health Service."—*U. S. P.*

For the purpose of immunization, the U. S. Pharmacopeia under "Tetanus Toxoid" states:

"Acti- toxoid is recommended for the treatment of tetanus. The recommended dose is injected subcutaneously, preferably in the region of the deltoid. Four to six weeks later the second and final injection is given. The immunity thus produced is reasonably persistent. However, it has been shown that, if some time after the original immunization a single injection of toxoid is given, there results a prompt (within two weeks) increase in the antitoxin titer of the serum. Thus

the immunity is maintained and the antitoxin titer is increased. This is the basis of the booster injection.

course is the administration of antitoxin. Active immunization against tetanus would appear to be a desirable procedure in the case of individuals who are subject to a greater than normal hazard of the disease.

LEDERLE LABORATORIES, DIVISION AMERICAN CYANAMID CO.

Tetanus Toxoid (Refined Alum Precipitated): 1 cc. and 10 cc. vials in packages of two 1 cc. vials (two immunizing doses), and of one 10 cc. vial (ten immunizing doses). Preserved with sodium ethylmercurithiosalicylate 1:10,000.

ELI LILLY AND COMPANY

Tetanus Toxoid (Alum Precipitated): 0.5 cc. and 5 cc. vials in packages of two 1 cc. vials (two immunizing doses), and of one 5 cc. vial (ten immunizing doses). Preserved with sodium ethylmercurithiosalicylate 1:10,000.

NATIONAL DRUG COMPANY

Tetanus Toxoid (Alum Precipitated): Two 0.5 cc. vials (one immunization), one 5 cc. vial (five immunizations) and

one 0.5 cc vial for supplementary dose Preserved with sodium ethylmercurithiosalicylate 1:10,000

PARKE, DAVIS & COMPANY

Tetanus Toxoid (Alum Precipitated Refined) Two 1 cc. vials (one immunization treatment) and one 10 cc vial (five immunization treatments)

PITMAN MOORE COMPANY, DIVISION OF ALLIED LABORATORIES INC.

Tetanus Toxoid (Alum Precipitated) 1 cc vials in packages of two 1 cc. vials (two immunizing doses) and 10 cc vial (ten immunizing doses) Preserved with sodium ethylmercurithiosalicylate 1:10,000

SHARP & DOHME INC

Tetanus Toxoid (Alum Precipitated Refined) 1 cc and 10 cc vials in packages of two 1 cc vials (one immunization) and of one 10 cc vial (five immunizations) Preserved with sodium ethylmercurithiosalicylate 1:10,000

E. R. SQUIBB & SONS

Refined Tetanus Toxoid (Alum Precipitated) 1 cc vials in packages of two each (two immunizing doses) 10 cc vials (ten immunizing doses) Preserved with sodium ethylmercurithiosalicylate 1:10,000

WYETH INCORPORATED

Tetanus Toxoid (Alum Precipitated Refined) 0.5 cc
0 immunizing
doses) 5 cc
nizing doses)
with sodium

Bacterial Vaccines

Bacterial vaccines or bacterins are suspensions of killed bacteria in physiological solution of sodium chloride usually with the addition of some preservative such as cresol or phenol.

The dosage and intervals for bacterial vaccine treatment cannot be stated definitely. In general the severer the disease the smaller the dose should be and the smaller the doses the shorter the intervals. In mild affections no improvement may result until the vaccine is pushed to a systemic reaction.

Prophylactically the typhoid and paratyphoid vaccines apparently have proved of great value as compared to other stock bacterial vaccines the therapeutic use of which often rests on uncertain clinical evidence. Plague and cholera vaccines are also used in prophylaxis.

BRUCELLA VACCINE.—Undulant Fever Vaccine.—A bacterial vaccine obtained from *Brucella melitensis* *Br. abortus*

Pertussis Vaccine (Phase I Concentrate): 20,000 million *H. pertussis* per cc., 5 cc. and 50 cc. vials. Preserved with phenol 0.25 per cent and sodium ethylmercurithiosalicylate 0.002 to 0.005 per cent.

THE NATIONAL DRUG CO.

Pertussis Vaccine: 40,000 million *H. pertussis* per cc., 2.5 cc. (one immunization) and 10 cc. vial (four immunizations). Preserved with sodium ethylmercurithiosalicylate 1:10,000.

PARKE, DAVIS & Co.

Pertussis Vaccine (Immunizing Sauer): 15,000 million *H. pertussis* per cc., 6 cc. and 24 cc. vials.

SHARP & DOHME, INC.

Pertussis Bacterin ("H" Strength): 20,000 million *H. pertussis* per cc., 5 cc. and 20 cc. vials. Preserved with phenol 0.5 per cent.

E. R. SQUIBB & SONS

Pertussis Vaccine (Single Strength): 10,000 million *H. pertussis* per cc., 8 cc. and 24 cc. vials. Preserved with phenol 0.5 per cent.

Pertussis Vaccine (Double Strength): 20,000 million *H. pertussis* per cc., 5 cc. and 20 cc. vials. Preserved with phenol 0.5 per cent.

THE UPJOHN COMPANY

Pertussis Vaccine (Single Strength): 10,000 million *H. pertussis* per cc., 24 cc. vials. Preserved with phenol 0.5 per cent.

Pertussis Vaccine (Double Strength): 20,000 million *H. pertussis* per cc., 5 cc. and 20 cc. vials. Preserved with phenol 0.5 per cent.

WYETH INCORPORATED

Pertussis Vaccine: 40,000 million *H. pertussis* per cc., 2.5 cc. and 10 cc. vials. Preserved with sodium ethylmercurithiosalicylate 0.01 per cent.

PERTUSSIS VACCINE ALUM PRECIPITATED.—

A bacterial vaccine prepared from alum precipitated, killed *H. pertussis*.

Actions and Uses.—Same as Bacterial Vaccine made from *H. pertussis*.

Dosage.—Three 1 cc. subcutaneous injections of 10,000 million or 15,000 million *H. pertussis* at three to four week intervals.

THE NATIONAL DRUG CO.

Pertussis Vaccine (Alum Precipitated): 30,000 million *H. pertussis* per cc., one 0.5 cc. vial (supplementary dose). Pre-

served with sodium ethylmercurithiosalicylate 1 10 000 For use as a booster dose to maintain a high protective level It is desirable to give a booster dose (0.5 cc) one year after primary immunization and again at school age

PARKS, DAVIS & Co

Pertussis Vaccine (Alum Precipitated Sauer) 30 000 million *H pertussis* per cc in 0.6 per cent solution of sodium chloride 1.5 cc. and 6 cc vials Preserved with sodium ethylmercurithiosalicylate 0.01 per cent

PERTUSSIS VACCINE AND ANTITOXIN, COMBINED — Pertussis Endotoxoid Vaccine — A suspension of *Hemophilus pertussis* phase 1 organisms in a solution of *H pertussis* endotoxoid The bacterial suspension is prepared after the technic of Kendrick and Eldering and the endotoxoid by the Stroom method

Actions and Uses — Pertussis endotoxoid vaccine is recommended for the active immunization of individuals who are susceptible to pertussis It is not intended for treatment of the disease or for the production of immunity once exposure has taken place

Dosage — For children 4 years of age and older a total amount of 6 cc. should be administered subcutaneously in four doses twelve to fourteen days apart as follows 1 cc., 1.5 cc., 1.5 cc., 2 cc. For children under 4 years of age the dose may be reduced for the initial injection a satisfactory dosage schedule consists of five injections also at twelve to fourteen day intervals as follows 0.5 cc., 1 cc., 1 cc., 1.5 cc., 1.5 cc. After completion of the preliminary course it is customary to give a fortifying dose of 2 cc. (one injection) each year up to 5 years of age When it is inconvenient to have the patient return for injections more than three times three injections can be given at twelve to fourteen day intervals as follows 1 cc., 2 cc., 2 cc. Dosage intervals of one month may be preferred in cases in which the additional length of time required for vaccination is not objectionable

PERTUSSIS VACCINE COMBINED WITH DIPHTHERIA TOXOID — A combination of pertussis vaccine with diphtheria toxoid

Actions and Uses — Employed in the simultaneous immunization of susceptible persons against diphtheria and whooping cough.

Dosage — Three doses of 1 cc. at three to four week intervals

THE NATIONAL DRUG Co

Diphtheria Toxoid Alum Precipitated and Pertussis Vaccine Combined 30 000 million *H pertussis* per cc. with diphtheria toxoid three 0.5 cc. vials (one immunization) and three 2.5 cc vials (five immunizations) Dosage Three 0.5 cc subcutaneous injections at four to six week intervals Preserved with sodium ethylmercurithiosalicylate 1 10 000

Actions and Uses—Pertussis vaccine combined with tetanus toxoid is employed for the simultaneous active immunization of persons susceptible to both these infections. The combination is suitable for initial basic immunization as well as for follow up stimulation because the dosage intervals for satisfactory results are similar for both antigens. It is intended primarily for use when it is considered expedient or preferable to administer diphtheria immunization separately.

Dosage—For basic immunization of infants, three subcutaneous injections consisting of 0.5 cc, 1.0 cc, and 1.0 cc are administered consecutively at intervals of one month. For use as a 'booster' to stimulate greater and more prolonged immunity, a single follow up dose of 1.0 cc is recommended one year after basic immunization has been completed.

CUTTER LABORATORIES

Tetanus Toxoid and Bacterial Vaccine Made from *H. pertussis* Combined 40 000 million phase I *H. pertussis* per cc, 2.5 cc (one complete immunization) and 10 cc (four complete immunizations) vials. Preserved with sodium ethylmercuri thiosalicylate 1:10 000.

PLAGUE VACCINE-U. S. P.—"A sterile suspension of killed plague bacilli (*Pasteurella pestis*), of a strain selected for high antigenic efficiency in isotonic solution of sodium chloride or other suitable diluent. The vaccine shall contain, in each cc at least 2 000 million plague organisms. Plague Vaccine complies with the requirements of the National Institute of Health of the United States Public Health Service"
U. S. P.

Actions and Uses—This vaccine has been used for the prevention of plague. The value of this vaccine is very doubtful.

Dosage—"Hypodermic, for active immunization, 0.5 cc and 1 cc, with a 7 to 10 day interval, the latter dose preferably to be repeated once"
U. S. P.

CUTTER LABORATORIES

Plague Vaccine 2 000 million killed bacilli 20 cc. vials

SMALLPOX VACCINE—Glycerinated Vaccine Virus—Jennerian Vaccine—Antismallpox Vaccine—Smallpox Vaccine consists of a glycerinated suspension of the vesicles of vaccinia or cowpox which have been obtained from healthy vaccinated animals of the bovine family. The vesicles must be removed and the vaccine must be prepared under aseptic conditions.

The vesicles must be removed from the animal at the time of

suitable development, thoroughly triturated and made into a smooth suspension with an aqueous solution of glycerin. This solution must not be acid to bromocresol purple T. S. and not distinctly alkaline to phenol red T. S. Smallpox vaccine complies with the requirements of the National Institute of Health of the United States Public Health Service." U. S. P.

Actions and Uses.—Smallpox vaccine acts by rendering the vaccinated person resistant to invasion by the virus of smallpox and is used in the prevention of that disease. The vaccine is administered by cutaneous insertion, preferably in the deltoid region, with a sterile needle which is held parallel to the cleansed skin and depressed quickly, breaking the epithelium, about 30 times through a drop of the vaccine. No dressing is to be employed.

STAPHYLOCOCCUS VACCINE.—Made from *Staphylococcus aureus*, from *Staphylococcus albus*, or from *Staphylococcus citreus*, or from all three.

Actions and Uses.—*Staphylococcus* vaccine is used in carbuncles, furunculosis, sycosis, and certain cases of acne. An autogenous vaccine is preferable, but if this cannot be made, a stock vaccine can be used with some prospect of success. The forms of acne most likely to respond are characterized by deep-seated pustules, with considerable induration, occurring on the face, chest and back. When the lesions are superficial and indolent, the acne bacillus vaccine may give good results.

Dosage.—100 million to 1,000 million killed bacteria.

ELI LILLY AND COMPANY

Staphylococcus Vaccine: 2,000 million killed *Staphylococcus aureus* per cc., 5 cc. vials. Preserved with sodium ethylmercurithiosalicylate 1:10,000

Staphylococcus Aureus Vaccine: 2,000 million killed *Staphylococcus aureus* per cc., 5 cc. vials. Preserved with sodium ethylmercurithiosalicylate 1:10,000

PARKE, DAVIS & COMPANY

Furunculosis Vaccine: 2,000 million killed *Staphylococcus aureus* per cc., 5 cc. and 20 cc. vials.

ROCKY MOUNTAIN SPOTTED FEVER VACCINE.—Vaccine prepared from membranes of embryonated chicken eggs infected with *Rickettsia rickettsii*. Rocky Mountain spotted fever vaccine is prepared from a saline suspension of infected

Actions and Uses—There is considerable amount of evidence that the vaccine is effective in the prevention of the disease.

andersoni which is rarely found in urban centers, while in the eastern United States both urban and rural areas may be in-

the vaccine should be employed depends to a large extent upon

cine contains egg protein, hence should not be given to persons sensitive to egg protein

Dosage—0.5 cc. to 2.0 cc., depending on the age of the subject, to be repeated once or twice at intervals of from 5 to 10 days.

E. R. SQUIBB & SONS

Rocky Mountain Spotted Fever Vaccine: 4 cc. vials. Preserved with sodium ethylmercurithiosalicylate 1:10,000

TYPHOID VACCINE-U. S. P.—"A sterile suspension in isotonic sodium chloride solution or other suitable diluent of killed *Salmonella typhi* (Eberthella typhi) of proven potency

third injection of the same size is given from seven to ten days after the second.

CUTTER LABORATORIES

Typhoid Vaccine (Prophylactic): 1 cc. bottles in packages of three, one containing 500 million and two each containing 1,000 million killed bacilli (strain 58, the Panama carrier strain). Preserved with tricresol 0.25 per cent.

ELI LILLY AND COMPANY

Typhoid Vaccine (Prophylactic): 1 cc. vials in packages of three, one containing 500 million and two each containing 1,000 million killed bacilli (strain 58, the Panama carrier strain). Preserved with sodium ethylmercurithiosalicylate 1:10,000.

NATIONAL DRUG COMPANY

Typhoid Vaccine: 1 cc. vials in packages of three, one containing 1,000 million and two each containing 2,000 million killed bacilli (strain 58, the Panama carrier strain); 5 cc. vials containing 2,000 million killed bacilli of the same strain per cubic centimeter. Preserved with sodium ethylmercurithiosalicylate 1:10,000.

PARKE, DAVIS & COMPANY

Typhoid Vaccine: 1 cc. vials in packages of three, one containing 500 million and two each containing 1,000 million killed typhoid bacilli Panama carrier strain 58.

Typhoid Vaccine: 5 cc. and 20 cc. vials containing 1,000 million killed typhoid bacilli Panama strain 58 per cc., 5 cc. and 20 cc. vials.

PITMAN-MOORE COMPANY, DIVISION OF ALLIED LABORATORIES, INC.

Typhoid Vaccine: 1,000 million killed typhoid bacilli (Panama carrier strain 58) per cc., 5 cc. and 20 cc. vials. Preserved with sodium ethylmercurithiosalicylate 1:10,000.

U. S. STANDARD PRODUCTS CO.

Typhoid Vaccine: 1 cc. vials in packages of three, one containing 500 million and two each containing 1,000 million killed bacilli (strain 58, the Panama carrier strain); 5 cc. and 20 cc. vials containing 1,000 million killed bacilli of the same strain per cc. Preserved with phenol 0.5 per cent.

Typhoid-Vaccine Mixtures

TOXOID-VACCINE MIX-
in each cubic centimeter 2,000
aureus and the staphylococcus
tizing doses of toxin.

Actions and Uses.—Staphylococcus toxoid-vaccine mixture is

used in infections of recognized staphylococcic etiology. Such a mixture has been offered to neutralize the toxin and effect lysis of the invading organism. Local reactions may follow injection.

Dosage—Ten doses, the first dose being 0.1 cc (200 million *Staphylococcus aureus*, staphylococcus toxoid 100 necrotizing doses), the tenth 10 cc. Each dose is increased by 0.1 cc. The agent is given subcutaneously at weekly intervals.

THE NATIONAL DRUG CO.

Vatox *Staphylococcus Toxoid-Vaccine* 6 cc vials. Preserved with sodium ethylmercurithiosalicylate 1:10,000.

DIAGNOSTIC AGENTS

Toxins for Immunity Tests

DIPHTHERIA TOXIN DIAGNOSTIC U. S. P.

Service U. S. P.

For description and regulations see the U. S. Pharmacopeia under Diphtheria Toxin Diagnostic.

Actions and Uses—This test is intended to determine those persons who are immune to diphtheria. In nonimmune persons

the toxin is absorbed and acts from 1 to 2 cm. 0.1 cc. of diphtheria forty-eight

hours, and is at its height in from forty-eight to seventy-two hours. It remains for from six to twelve days, is followed by slight scaling and leaves a brownish, pigmented spot. In some

Dosage—"Intracutaneous for determining susceptibility (Schick Test), 0.1 cc. of the dilution, representing one fiftieth of the minimum lethal dose" U. S. P.

CUTLER LABORATORIES

Diphtheria Toxin for the Schick Test (Diluted): 1 cc. vial containing sufficient diluted toxin for 10 tests. Preserved with 0.5 per cent phenol.

LEDERLE LABORATORIES, DIVISION AMERICAN CYANAMID CO.

Diphtheria Toxin for Schick Test (in Peptone Solution): 1 cc. and 5 cc. vials, containing sufficient diluted toxin for 10 and 50 tests, respectively; also in the form of heat treated peptone-diluted toxin in a package containing sufficient material for 10 control tests respectively.

ELI LILLY AND COMPANY

Diphtheria Toxin for Schick Test (Diluted): 1 cc. and 10 cc. vials containing sufficient diluted toxin for 10 and 100 tests, respectively, in isotonic solution of sodium chloride containing 0.1 per cent gelatin.

NATIONAL DRUG COMPANY

Diphtheria Toxin for Schick Test (Diluted): 1 cc, 5 cc. and 10 cc. vials containing sufficient diluted toxin for 10, 50 and 100 tests, respectively. Preserved with sodium ethylmercurithiosalicylate 1:10,000.

PARKE, DAVIS & COMPANY

Diphtheria Toxin for Schick Test (Diluted): 1 cc., 5 cc., 10 cc. and 50 cc. vials containing sufficient diluted toxin for 10, 50 and 100 tests, respectively. Preserved with sodium ethylmercurithiosalicylate 1:10,000.

diluted toxin for control tests.

PITMAN-MOORE COMPANY, DIVISION OF ALLIED LABORATORIES, INC.

Diphtheria Toxin for the Schick Test: 1 cc. vial containing sufficient diluted toxin for 10 tests. Preserved with phenol 0.5 per cent.

SHARP & DOHME, INC.

Diphtheria Toxin for the Schick Test (Diluted): 1 cc, 5 cc. and 10 cc. vials containing sufficient diluted toxin for 10, 50 and 100 tests, respectively; also supplied in the form of heat treated diluted toxin in 5 cc. vial containing sufficient material for 50 control tests.

E. R. SQUIBB & SONS

Diphtheria Toxin for the Schick Test (In Peptone Solution): 1 cc. vials containing sufficient diluted toxin for 10 tests, preserved with phenol 0.5 per cent.

WYETH, INCORPORATED

Diphtheria Toxin for the Schick Test (Diluted): 1 cc., 2.5 cc. and 5 cc. vials containing sufficient diluted toxin for 10, 25 and 50 tests, respectively; also in the form of heat treated diluted toxin in vials containing sufficient material for 10, 25 and 50 control tests, respectively.

SCARLET FEVER STREPTOCOCCUS TOXIN FOR DICK TEST.—For definition see this title under Bacterial Toxins

Actions and Uses—The toxin of the hemolytic streptococcus of scarlet fever is used for determination of susceptibility to

at the end of twenty-four hours are regarded as negative. Positive reactions fade rapidly and have usually disappeared at the end of from forty eight to seventy-two hours

Scarlet fever streptococcus toxin diluted for use will retain its potency for at least two months at room temperature

LEDERLE LABORATORIES DIVISION AMERICAN CYANAMID CO

Scarlet Fever Streptococcus Toxin for the Dick Test
2 cc. and 10 cc. vials containing sufficient diluted toxin for withdrawal to perform 5 and 50 tests, respectively Preserved with phenol 0.4 per cent

NATIONAL DRUG COMPANY

Scarlet Fever Streptococcus Toxin for the Dick Test
2 cc. and 11 cc. vials containing sufficient diluted toxin for withdrawal to perform 5 and 50 tests respectively Preserved with phenol 0.4 per cent

PARKE, DAVIS & COMPANY

Scarlet Fever Streptococcus Toxin for the Dick Test
2 cc. vials containing sufficient diluted toxin for withdrawal to perform 5 tests

Scarlet Fever Streptococcus Toxin for the Dick Test
10 cc. vial containing sufficient diluted toxin for withdrawal to perform 50 tests

SHARP & DOHME INC

Scarlet Fever Streptococcus Toxin for the Dick Test
2 cc ampuls containing sufficient diluted toxin for withdrawal to perform 5 tests

Scarlet Fever Streptococcus Toxin for the Dick Test
10 cc vial containing sufficient diluted toxin for withdrawal to perform 50 tests

E. R. SQUIBS & SONS

Scarlet Fever Streptococcus Toxin for the Dick Test
2 cc and 11 cc vials containing sufficient diluted toxin for with

drawal to perform 5 and 50 tests, respectively. Preserved with phenol 0.3 per cent.

U. S. STANDARD PRODUCTS Co.

Scarlet Fever Streptococcus Toxin for the Dick Test: 2 cc. ampules containing sufficient diluted toxin for withdrawal to perform 5 tests and 11 cc. vial ampuls containing sufficient diluted toxin for withdrawal to perform 50 tests. Preserved with phenol 0.4 per cent.

WYETH, INCORPORATED

Scarlet Fever Streptococcus Toxin for the Dick Test: 2 cc. and 10 cc. vials containing sufficient diluted toxin for withdrawal to perform five and fifty tests, respectively. Preserved with phenol 0.4 per cent.

SCARLET FEVER STREPTOCOCCUS ANTITOXIN NON-VEGETABLE ORIGIN

(under Antitoxins.)

Actions and Uses—The antitoxic serum of the hemolytic streptococcus of scarlet fever which is used to produce temporary passive immunity and in the treatment of the disease is also used in the performance of a skin test to differentiate the rash of scarlet fever from eruptions due to other causes. When doubt exists as to the nature of the eruption in cases where a diagnosis of scarlet fever cannot otherwise be ruled out, a small dose of not more than 0.2 cc. (containing 2,000 to 5,000 original neutralizing units) of the antitoxin is injected intracutaneously in the exanthematous area for the test. A positive reaction is known as the Schultz-Charlton phenomenon and consists in the more or less complete disappearance of the rash over an area of 2 cm. or more in diameter at the site of injection within four to twenty-four hours. This reaction is characteristic of scarlet fever and is caused only by scarlet fever antitoxin.

TUBERCULINS.—Many different methods have been used to prepare from the tubercle bacillus (*Mycobacterium tuberculosis*) substances which might be used in the diagnosis or treatment of tuberculosis. These have been, in general, called tuberculins, and a few of the more prominent are enumerated here. For diagnosis, either Koch's old tuberculin or a preparation from the filtrate of a synthetic nonprotein culture medium in which tubercle bacilli have been grown, is usually employed. For treatment, each tuberculin has its advocates, but it is doubtful whether there is any essential difference in the action of the various forms. The strength varies, however, not only in tuber-

tulins prepared by different methods, but also in different batches prepared in exactly the same manner. A tuberculin, designated Purified Protein Derivative, has been prepared within the last

people who have been infected do not react, and this fact must

as a measure of economy, obviating the necessity of the most costly examination.

In recent years the use of tuberculin in the treatment of

nary cases. Treatment is generally carried out by beginning

first, in the fact that the substance, properly used, causes a mild focal reaction at the site of infection leading gradually to fibrosis, and second, in the fact that frequently repeated injec-

tuberculin. This susceptibility varies enormously in different individuals and at different stages of the treatment, entirely out of relation to the progress of the disease. The use of tuberculin in treatment therefore requires special knowledge and experience. The doses ordinarily used in diagnosis rarely lead to constitutional reaction.

PITMAN-MOORE COMPANY, DIVISION OF ALLIED LABORATORIES, INC.

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PURIFIED PROTEIN DERIVATIVE OF TUBERCULIN-U. S. P.—"A sterile, soluble product of the growth of tubercle bacillus (*Mycobacterium tuberculosis*) prepared in a special liquid free from protein. Purified Protein Derivative of Tuberculin complies with the requirements of the National Institute of Health of the United States Public Health Service." U. S. P.

For description and regulations see the U. S. Pharmacopeia under Tuberculin, Purified Protein Derivative.

The method of administration is the Mantoux test described under the heading Old Tuberculin. Intracutaneous injection is made, as with old tuberculin, but instead of the doses given for old tuberculin, standard doses of 0.00002 mg. and 0.005 mg. of purified protein derivative of tuberculin are employed. The method of reading reactions is the same as that given in the section on old tuberculin.

PARKE, DAVIS & COMPANY

Tablets Tuberculin, Purified Protein Derivative (First Strength): Packages containing 2 vials (5 tests each) and 1 cc. vial of sterile diluent; and packages containing 10 tablets (100 tests) with 10 cc. vial of diluent.

Tablets Tuberculin, Purified Protein Derivative (Second Strength): Packages containing 2 vials (5 tests each) and 1 cc. of sterile diluent; and packages containing 10 tablets (100 tests) with 10 cc. vial of diluent.

Tablets Tuberculin, Purified Protein Derivative (First and Second Strength): Sufficient for 20 tests each of first and second strength. Packages for individual testing containing 2 vials, 1 tablet each of first strength and 2 vials, 1 tablet each of second strength with a 5 cc. vial of sterile diluent.

OLD TUBERCULIN-U. S. P.—Tuberculin-Koch.—Concentrated Tuberculin—Crude Tuberculin.—"A sterile solution in a special liquid culture medium of the soluble products of growth of the tubercle bacillus (*Mycobacterium tuberculosis*) and should contain about 50 per cent of glycerin. Old Tuberculin

Actions and Uses—For diagnosis, old tuberculin is used most commonly by intracutaneous injection (Mantoux test) or cutaneously by application to a scarified spot on the skin (von Pirquet test). It may also be used in the form of an ointment or paste applied directly (Moro test) or through the medium of an absorbent material or patch (patch test). The latter method has gained in popularity in recent years. Inflammation at the site of injection is usually moderate, and the patient has no systemic reaction. The reaction is

commonly employed. Concentrated old tuberculin is diluted under sterile precautions, so that 0.1 cc (the quantity to be injected) will contain 0.01 cmm of old tuberculin (commonly but erroneously called 0.01 mg). Dilution of the tuberculin should be made on the day of test.

The diluted material should be injected intracutaneously into the skin of the flexor surface of the forearm. A 1 cc syringe

In
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the

opposite forearm. Occasionally, for extra precaution, an intermediate dose of 0.1 cmm is employed and sometimes this dose only is used. The latter practice saves time but occasionally moderately severe reactions may occur, and it is generally recognized that a number of persons who would be positive to 10 cmm do not react to 0.1 cmm. In the absence of a reaction following the last dose of tuberculin, the patient is regarded as negative. The reaction consists in a papule of edema 5 mm in diameter with a surrounding zone of redness at the point of the tuberculin injection. If there is no edema or induration the reaction should be considered negative. This reaction ordinarily reaches its height in forty-eight hours.

Unclassified Therapeutic Agents

This chapter is created as a repository for agents of definite value that cannot logically be described with those classified as having a common therapeutic purpose.

2,3-DIMERCAPTOPROPANOL IN OIL.—Bal in Oil (H. W. & D.).—A solution of 2,3-dimercaptopropanol 10 per cent in peanut oil, containing benzyl benzoate 20 per cent. The structural formula of 2,3-dimercaptopropanol may be represented as follows:



For tests and standards, see Section B.

Actions and Uses.—2,3-Dimercaptopropanol in oil is indicated in the treatment of arsenic, gold and mercury poisoning. Results in the treatment of other heavy metal poisoning such as antimony and bismuth have been inconclusive and results in lead poisoning have been disappointing.

2,3-Dimercaptopropanol, by virtue of being a dithiol, competes with physiologically essential cellular -SH groups for arsenic, mercury, and gold, thus preventing combination of the heavy metal with these groups. The stable combination of 2,3-dimercaptopropanol and heavy metal is rapidly excreted and the body thus freed quickly of the toxic agent.

2,3-Dimercaptopropanol is particularly useful in the treatment of massive arsenic poisoning, possibly postarsenical following parenteral treatment of agranulocytosis due to arsenic but other measures, principally massive doses of penicillin, must also be employed.

While 2,3-dimercaptopropanol in oil is indicated in the treatment of mercury poisoning, it must be remembered that mercury causes rapid and extensive tissue damage, particularly to the kidneys, which cannot be corrected by the administration of 2,3-dimercaptopropanol. The use of 2,3-dimercaptopropanol

in oil in the treatment of mercury poisoning is still in the experimental stage and definite recommendations cannot be made.

The toxicity of 2,3-dimercaptopropanol appears to be less in patients suffering from arsenic, gold or mercury poisoning but doses of 300 mg (5 mg per kilogram of body weight) may produce nausea, vomiting and headache, a burning sensation of the lips, mouth, throat and eyes, generalized muscular aches with burning and tingling of the extremities, and a sense of constriction in the chest. The symptoms usually subside in 30 to 90 minutes.

Dosage—In the treatment of arsenic or gold poisoning, 3 mg per Kg of 2,3-dimercaptopropanol (as a 10 per cent solution in oil) should be administered by intramuscular injection every four hours for the first two days, four injections on the third day and injections twice daily thereafter for ten days or until complete recovery. In milder cases the dose may be reduced to 2.5 mg per Kg.

HYNSON, WESTCOTT & DUNNING, INC.

Solution Bal in Oil 2,3-dimercaptopropanol 10 per cent and benzyl benzoate 20 per cent in peanut oil 4½ cc ampuls

GOLD COMPOUNDS

The clinical use of gold salts in the treatment of arthritis has been in vogue since 1927 and since 1935 has come to be rather generally recognized as having some value in selected and carefully supervised cases of progressive rheumatoid arthritis unrelieved by older and safer methods of treatment. Its mechanism is not understood. According to the editorial review of Philip S. Hench (*Annals of Internal Medicine* 6:618, 1947) somewhat over half of the reported patients obtain symptomatic relief completely in up to a sixth. Up to three-fourths of the improved cases relapse after a time but may again improve under further treatment. The improvement usually does not begin until the gold injections have been continued for one to three months. This makes it difficult to assign a specific value to the gold treatment, especially as rheumatoid arthritis is potentially reversible without gold. Some skeptical observers consider the results about equal with or without gold, but more are inclined to conclude that gold plays a positive role since the successes have generally been scored on patients in whom other measures have failed. The few control series including a blindfold test also note improvement rates of some five to ten times higher with gold than without. However, these chances of usually partial success must be weighed against the risk of very serious toxic reactions in some five per cent of the patients. Minor or moderate transient toxicities develop in nearly half the cases.

For several years the Council has recognized the use of gold salts by injection for the systemic treatment of nondisseminated

lupus erythematosus and considers the intramuscular route, i.e., intragluteal injection, to be the preferred method of administration to obtain the systemic effects of gold compounds. Gold is thus eliminated by the kidneys and at a much slower rate than it is injected, so that a large cumulation remains in the system for as long as a year after treatment is discontinued. On this account and because of the high incidence of reactions (up to 40 or 50 per cent) attributable to the extremely large doses formerly employed in rheumatoid arthritis (100 to 500 mg. for a total of 1.5 to 2 Gm. in a single course of treatment), the Council was previously hesitant to recognize the use of gold salts for the treatment of that disease.

The advent of more conservative dosage for the treatment of rheumatoid arthritis has greatly reduced the rate of reactions, especially the incidence of serious toxic effects. Rather than the enormous dosages formerly employed, experience has shown that therapy should be started with doses of not more than 25 mg. calculated on gold content and continued with gradually increased doses of not more than 50 mg. for women and 75 mg. for men, at weekly intervals, for a total of 500 to 1,000 mg. for a single course of treatment. A total dosage of up to 2,000 mg. is sometimes recommended, but it should be kept in mind that the higher the dosage employed, the greater the chance of reactions—perhaps severe or even fatal in character. Because of this danger, the patient should be examined closely at each visit and a white blood count with differential taken every two or three weeks. The blood sedimentation rate of fall is a good indication of the effects of therapy.

Toxic reactions to gold are of the type seen after other heavy metals, notably arsenicals. The ones mostly to be feared are exfoliative dermatitis, agranulocytosis, purpura and hepatitis. Any skin reaction should demand immediate cessation of further gold therapy and it is doubtful that any patient who has once had a severe reaction should be subjected to further gold therapy. Nitritoid reactions similar to those seen after arsenicals are sometimes encountered. "Gold bronchitis" and polyneuritis have also been observed. Isolated cases of pigmentation have been reported. Patients should be warned of the deleterious effects of exposure to strong sunlight and should not be given actinotherapy as long as the possibility of photosensitization exists.

2,3-Dimercaptopropanol (BAL) has been used in the treatment of dermatitis due to aurotherapy. Further discussion of

value for the chronic stages of rheumatoid arthritis after the development of extensive deformities has occurred

GOLD SODIUM THIOMALATE — Myochrysine (MERCK) — Disodium aurothiomalate — A gold salt formed by the interaction of sodium thiomalate and a gold halide. It contains about 50 per cent of gold.



For tests and standards see Section B

Actions and Uses — Gold sodium thiomalate like other gold salts, is indicated for the treatment of established cases of active rheumatoid arthritis and for the treatment of nondisseminated lupus erythematosus. Against rheumatoid arthritis it is most effective in relatively early cases before development of extensive deformities. Gold sodium thiomalate is of no value in the treatment of other arthritides. See also the statement on Gold Compounds.

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MERCK & Co. INC.

Solution Myochrysine 10 mg., 25 mg. 50 mg. or 100 mg. of gold sodium thiomalate equivalent to 5 mg. 12.5 mg. 25 mg. and 50 mg. of gold respectively. 1 cc. ampuls.

U. S. patent 1,994,213 (March 12, 1935 expires 1952) and U. S. trademark 318,890 both assigned to Société des Usines Chimiques Rhône-Poulenc Paris France.

GOLD AND SODIUM THIOSULFATE N. F. — $\text{AuNa}_3(\text{S}_2\text{O}_3)_2 \cdot 2\text{H}_2\text{O}$. The complex salt formed from 1 molecule of gold thiosulfate and 3 molecules of sodium thiosulfate.

Contains not less than 36.7 per cent and not more than 37.7 per cent of Au [gold] — N. F.

For description and standards see The National Formulary under Gold and Sodium Thiosulfate.

Actions and Uses — Gold sodium thiosulfate is used for the treatment of nondisseminated lupus erythematosus and of active

rheumatoid arthritis. Its action in these conditions is nonspecific, but has proved beneficial in some cases. It is of no value in chronic forms of arthritis and should not be used in acute rheumatic fever. Also see statement on Gold Compounds.

Even when the doses administered are small, accidents have occurred. The reactions most commonly encountered are varying degrees of fever, diarrhea, vomiting, albuminuria, enteritis, stomatitis, prostration and shock. Skin reactions consist of varying degrees of erythema, urticaria, severe papular and vesicular dermatitis, and scarlatiniform and exfoliative dermatitis. Cases of aplastic anemia, of hemorrhagic diathesis, and of agranulocytosis have also been noted following its use. Published necropsy reports reveal conditions usually found in heavy metal poisoning. A certain number of cases of toxic hepatitis and of acute yellow atrophy have been noted after the use of this drug, likewise isolated cases of generalized pigmentations. Patients to whom gold salts are being administered should be warned of possible deleterious effects from strong sunlight. Moreover, they should not be given actinotherapy.

Dosage.—For localized lupus erythematosus the initial dose preferred is 5 mg. intramuscularly given in from 2 to 5 cc. of sterile distilled water. For ~~active~~ rheumatoid arthritis the initial dose should not exceed 2½ mg. intramuscularly, given 3 or 4 times a week, kept within the same limit. For ~~active~~ rheumatoid arthritis the initial dose should not exceed 500 to 1000 mg. for men and 250 to 500 mg. for women, at weekly intervals are increased 5 mg. per dose, not exceeding a maximum of 50 mg. for women and 75 mg. for men, provided no reactions have occurred. The drug may be continued cautiously in smaller dosage following complete recovery from mild reactions but should be discontinued permanently if severe reactions have occurred.

ABBOTT LABORATORIES

Solution Gold Sodium Thiosulfate: 10 mg., 25 mg., 50 mg., 75 mg., 0.1 Gm. ampuls.

MERCK & Co., INC.

Solution Gold Sodium Thiosulfate: 10 mg., 25 mg., 50 mg. ampuls and 75 mg. and 100 mg. bottles

G. D. SEARLE & Co.

Solution Gold Sodium Thiosulfate with Sodium Thiosulfate and Benzyl Alcohol 2%: Gold sodium thiosulfate 50 mg., sodium thiosulfate U. S. P. 278 mg., sodium sulfite 88 mg. and benzyl alcohol 2 per cent, 5 cc. serum-type vials.

Vitamins and Vitamin Preparations

For Prophylactic and Therapeutic Use

VITAMINS

The investigations of nutrition that have been initiated since the second decade of the present century have afforded an entirely new outlook upon many disorders some of which have long been suspected to be of dietary origin. This is due to the scientific demonstration that factors other than proteins carbohydrates fats and minerals are essential for the preservation of bodily well being and physiologic function. These factors are designated at the present time as vitamins.

The absence of any one of the vitamins from a diet which is satisfactory in other respects leads to the development of a typical syndrome which is called a deficiency disease. These diseases may be as striking in their manifestations as are the direct result of underfeeding (caloric deficiency) or deprivation of essential inorganic elements such as iodine iron calcium or phosphorus. A striking illustration of a deficiency disease is presented by scurvy. This can be entirely averted or effectively cured by the inclusion of foods which contain vitamin C (ascorbic acid) in the diet. It has been clearly established by convincing experiments that the prophylactic or remedial agent—the antiscorbutic substance—is a definite chemical entity having the composition $C_6H_8O_6$. The vitamin is present in many articles used as food such as fresh vegetables and fruits yet entirely lacking in others such as the common cereals and grains. Ascorbic acid is readily destroyed by heat under certain conditions notably in an alkaline medium and in the presence of oxygen. However foods can be processed without serious loss of ascorbic acid if precautions are taken to exclude air and if the pH of the food is not unfavorable for the preservation of the vitamin.

The foregoing illustration will suffice to indicate the characteristics of a vitamin—a substance essential for maintenance of normal metabolic functions not identical with the more familiar nutrients not synthesized in the human body in normally adequate amounts and therefore to be furnished by an exogenous supply sometimes more labile than the foodstuffs proper and

hence subject to deterioration, and distributed variously among the edible parts of animals and plants. More than twenty

physiologic properties as the naturally-occurring compounds.

For convenience the designations, vitamins A, B, C and D etc., have arisen. Scurvy, beriberi, rickets, pellagra, and xerophthalmia have been attributed with considerable experimental certainty to the lack of specific vitamins; the protective or curative substances are accordingly sometimes spoken of as the antiscorbutic vitamin (C), the antineuritic vitamin (B_1), the antirachitic vitamin (D), the pellagra-preventing vitamin, and the antixerophthalmic vitamin (A), etc. Detailed accounts of the physiology of the vitamins can now be found in the newest textbooks on physiological chemistry and nutrition. The problems raised thereby are the subject of active discussion and extensive investigation so that with respect to many features only tentative conclusions should be announced at this time.

Chemical, physical and microbiologic methods are now in general use for the determination of vitamins in pharmaceutical products, but, biologic assays must be used for vitamin D and for checking other determinations. To facilitate such assays and to make uniform the expression of vitamin content, the World Health Organization of the United Nations has sponsored the preparation and distribution of standards for vitamins A, B_1 , C and D. The International unit for each of these vitamins is defined in terms of the biological activity of a specific quantity of the respective standard. The U. S. P. units for vitamins A, B_1 , C and D are identical in value with the International units. The United States Pharmacopoeial Convention also distributes prototype standards for these four vitamins, and in addition reference standards for riboflavin and nicotinic acid.

The Council has decided that when practicable, vitamin content should be stated in milligrams in preference to micrograms or units. This action was prompted by recognition that confusing practices have grown up in the industry concerning representations for the vitamin content of products. The vitamin content of some products has therefore been expressed in micrograms even though the term is wholly unfamiliar to the laity. As a result of this the purchaser may be led to believe that a product has a higher vitamin content when so represented than if units or milligrams were used. For instance one milligram of vitamin B_1 equals 333 U. S. P. or International Units, or 1,000

U. S. P. units.

In recent years considerable information has been acquired

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supply of the requisite vitamins. Furthermore, with the exception of pellagra, there is no evidence of any noteworthy prevalence in this country of conditions in adults that might properly be ascribed to a severe deficiency of one or more vitamins. However, it must be admitted that under circumstances bringing about a highly restricted dietary regimen and leading to 'one-sided' diets a relative shortage of some of the vitamins does at times arise. In almost all such instances the situation can be properly corrected by prescription of appropriate foods. Occasionally and particularly with infants a corrective result may be more effectively secured by the administration of products especially rich in the desired vitamin—for example, cod liver oil as a dietary adjunct in the prevention or treatment of rickets and orange juice in the relief of scurvy.

The clear indications for such specific vitamin therapy are still few in number. The chief justification for the recognition of special vitamin-bearing products at present applies to unusual concentrations of the desired potent principle that they may represent or to exceptionally desirable dosage forms. Multi-vitamin preparations, particularly capsules, have come into very extensive use in recent years. In most of these preparations the proportion of vitamins present has borne no relationship to established therapeutic dosages nor to normal requirements for the vitamins. For various reasons the Council has opposed the use of such preparations. The Council will consider for acceptance vitamin content is
ns. This subject
(119 948 July

to 1942)

General Provisions and Labeling Requirements

Statement of Vitamin Potency—When vitamin A or vitamin D potency is expressed it must be in U. S. P. units. When the vitamin content of preparations of ascorbic acid, thiamine, riboflavin, nicotinic acid, nicotinamide, pyridoxine, menadione and similar vitamin K preparations is expressed it must be in milligrams and not in micrograms, gammas or units.

Vitamin preparations which supply in the recommended daily intake not more than three times the minimum daily requirements set forth in regulations under Section 403 (j) of the Food Drug and Cosmetic Act must be labeled to show the proportion of the minimum daily requirements supplied in the

To meet the requirements of the Food, Drug and Cosmetic Act with respect to adequate directions for use, such preparations must bear the statement ". . . daily, or as prescribed by the physician. This dosage is in excess of the quantity needed for prevention of . . . deficiency," or a more detailed statement of directions for use.

The above labeling requirements are exemplified in the following outline of statements which should appear on the main panel of the label:

STATEMENTS REQUIRED ON MAIN LABEL

For Preparations Supplying More Than Three Times the Minimum Daily Requirements

Quantity of contents:	50 tablets
Common or usual name:	Thiamine Hydrochloride Tablets
Quantity of vitamin in tablets consumed daily:	10 milligrams
Adequate directions for use:	Dose: One tablet daily, or as prescribed by the physician. This dosage is in excess of the quantity needed for prevention of thiamine deficiency.
Name and place of business:	John Doe 550 Broad Street Chicago, Illinois

For Preparations Supplying Three Times the Minimum Daily Requirements or Less

Quantity of contents:	100 tablets
Common or usual name:	Thiamine Hydrochloride Tablets
Quantity of vitamin in tablets consumed daily:	1 milligram
Dose:	This is optional
Proportion of minimum daily requirement:	1 tablet will supply the minimum daily requirement for an adult.
Name and place of business:	John Doe 550 Broad Street Chicago, Illinois

GENERAL ALLOWABLE CLAIMS FOR VITAMINS

Growth.—A deficiency lead to retardation of gro. vitamins but it is equal acids, minerals, and of conveying the impressio

night-blindness, or nyctalopia. For this type of night blindness vitamin A is a specific. Cases of nyctalopia exist which do not respond to treatment with vitamin A. These may be due to congenital defects or to other diseases than avitaminosis "A." In view of present knowledge, the claim is not acceptable that the administration of vitamin A to drivers of automobiles will diminish the chance of accident from driving at night.

3. Vitamin A is reported to be effective in the treatment of certain types of hyperkeratosis of the skin of persons suffering from severe deficiency of vitamin A.

4. Vitamin A in excess of normal requirements has not been shown to be of value in the prevention of colds, influenza and such infections.

5. There is at the present time inadequate evidence to warrant the claim that the ingestion of sufficient vitamin A will prevent the formation of renal calculi in man or that it is useful in the treatment of hyperthyroidism, anemia, degenerative conditions of the nervous system, sunburn, or ulcerative conditions of the skin.

The Vitamin B Complex

The term Vitamin B Complex is applied to a group of substances which have been shown to be constituents of what was formerly called vitamin B. Intensive investigations have produced an ever changing picture of the constituents which comprise the complex. At this writing eight compounds recognized as members of the vitamin B complex have been identified and

They are:

chloride (vitamin
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ion on Thiamine,

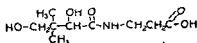
Riboflavin, a component of an oxidation-reduction system of living cells. See following section.

Nicotritional factor effective in the treatment of human pellagra. See following section on Nicotinic Acid and Nicotinic Acid Amide for further discussion.

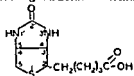
Pyridoxine (Vitamin B₆) or Pyridoxine Hydrochloride (vitamin B₆ hydrochloride), a factor for the prevention of nutritional dermatosis in rats. There is yet no satisfactory evidence relating to its therapeutic value for man.

Pantothenic Acid, a factor for the prevention of nutritional dermatosis in chicks and necessary for the growth of rats. Its value in human nutrition has not been demonstrated.

Pantothenic acid has the following structural formula:



Biotin has the following structural formula:



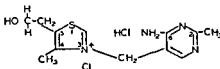
This compound combines with a protein-like substance in raw

ments may be synthesized in the intestinal tract.

Folic acid is a factor found effective in the treatment of macrocytic anemia. For further information see monograph on Folic Acid.

In addition to these eight compounds there are other factors that have been shown to be essential nutrients for a few species of experimental animals. None of these has been shown to have any importance in human nutrition.

THIAMINE



The International Conference on Vitamin Standardization has
 established the hydrochloride as the standard
 for biological activity.

Allowable Claims—1 Thiamine is of value in correcting and preventing beriberi.

The general opinion of the students of beriberi is that this disease with its nervous and cardiovascular manifestation is due primarily to an insufficient supply of thiamine. It is probable that in the majority of instances of human beriberi there are also deficiencies of food constituents other than thiamine. There

are conditions which probably could be designated as "latent beriberi"; it does not seem wise at this time to attempt the formulation of a definite statement covering such conditions other than that presented in Item 5.

2. Thiamine may be cited as of value in correcting and preventing anorexia of dietary origin in certain cases.

There are many causes of anorexia, some referable to infections and the reactions thereto, others to organic disorders, and still others related to faulty diet. Where there is no rather obvious cause of anorexia in question, other than a possible dietary one, it is permissible to claim that thiamine may be of therapeutic value when the condition to be treated is due to a deficiency of that vitamin.

3. The administration of thiamine in excess of that present in the ordinary diet may be advantageous when there are specific conditions indicating interference with proper assimilation of the vitamins.

The present status of research on the clinical use of thiamine for specific diseases other than beriberi and for infant feeding, is such that *definite* claims for therapeutic value in relation to such diseases cannot be recognized. Its use may be indicated, however, in such restricted conditions as pernicious vomiting of pregnancy, tube feedings through a jejunal fistula, and the like, because the above permitted statement applies to such conditions and gives an intelligent basis for such therapy.

4. While it has not been established that thiamine deficiency is the sole cause of conditions described as alcoholic neuritis, the neuritis of pregnancy and the neuritis of pellagra, there is some definite evidence of the value of this vitamin in the treatment of these conditions. Vague representations with respect to the value of thiamine in the treatment of other types of neuritis are not permissible.

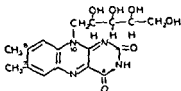
5. Thiamine deficiency in animals is associated with dysfunctions of the heart and of the vascular system. Thiamine is effective in reestablishing the normal function of the cardiovascular system if the dysfunction was caused by thiamine deficiency. Evidence is lacking that thiamine is effective in any other type of heart disease. At times organic heart disease and beriberi heart coexist. Administration of thiamine is justified in these patients.

6. It appears that there is an increased requirement for thiamine when there is greatly augmented metabolism such as occurs in febrile conditions, hyperthyroidism, or vigorous muscular activity.

7. Claims for concentrates containing thiamine offered for clinical use should state the potency of this agent in terms of milligrams. The term "concentrate" or a synonym will not be recognized if the product does not exceed a potency of 0.075 mg. per gram (or per cubic centimeter), or if it is a natural product which may have been subjected to a process of dehydration.

Riboflavin

Riboflavin, the empirical formula of which is $C_{17}H_{20}N_4O_6$, was formerly known as Vitamin G, Vitamin B₂ or Lactoflavin. The chemical nature of the vitamin was established in 1935. In 1936 the Council voted to accept riboflavin for purposes of



Allowable Claims—1 Riboflavin is recognized as a specific in the treatment of certain characteristic lesions of the tongue, the lips, and the face. The symptoms may be described briefly as follows. A typical glossitis may often be observed before other signs of riboflavin deficiency are present. In contrast to the glossitis of pellagra, the tongue is clean, the papillae are flattened or mushroom shaped rather than atrophic and the color is definitely purplish red or magenta instead of being scarlet as in nicotinic acid deficiency. As the disease pro

phobia. The anatomical changes may vary from a superficial invasion of the cornea by capillaries to an extensive vascular

Nicotinic Acid and Nicotinamide

Nicotinic acid ($C_6H_5O_2N$) and nicotinamide ($C_6H_5ON_2$) are of fundamental importance in the treatment of pellagra. The terms, niacin and niacin amide are now officially recognized as synonyms for these chemical names. The pure compounds

have been known for many years, but not until recently were they recognized as therapeutic agents. In 1938 the Council voted to accept nicotinic acid and nicotinamide "for purposes of standardization and clinical experimentation." Sufficient evidence has now been accumulated to demonstrate the usefulness of these drugs. Administration of relatively large doses of nicotinic acid produces a marked flushing of the face and neck sometimes associated with an unpleasant sensation, but the reaction is transient and apparently harmless. The effect is not observed following the administration of nicotinamide. For parenteral use nicotinamide is the drug of choice.

Nicotinic acid has the following structural formula:

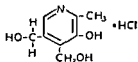


Nicotinamide has the following structural formula:



Allowable Claims.—1. Nicotinic acid and nicotinamide are recognized as specifics only in the treatment of pellagra. Their administration in appropriate doses lead to the disappearance of all alimentary, dermal, and other lesions, characteristic of the disease, to a return to normal of the porphyrin and porphyrin-like pigments of the urine, and to a profound improvement in the mental symptoms when the latter are the result of an inadequate intake of nicotinic acid and nicotinamide. These compounds are without influence upon the polyneuritis or cheilosis so frequently observed in pellagrous patients. In such cases it may be necessary to insure the presence in the diet of food, rich in vitamin B₁ or B₂, or to administer thiamine hydrochloride, riboflavin or both.

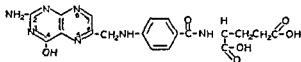
Pyridoxine



definite claims will be permitted. Pyridoxine is accepted to assure the availability of a preparation of satisfactory composition for investigational use.

Folic Acid

Folic acid has been referred to as 'Vitamin M' 'L. casei Factor' 'Vitamin B₁₂' and Folic Acid. The chemical name of the synthetic compound has been abbreviated to pteroylglutamic acid. The structural formula for the synthetic compound is



Folic acid produces a response when used in the treatment of pernicious anemia and some other macrocytic anemias in man and in experimental macrocytic anemias due to dietary deficiencies in monkeys, growing chicks and in fish.

Only a small portion of the folic acid found in many foods occurs in the free form and it is not yet clear to what extent the combined

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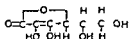
macrocytic anemias contain only traces of folic acid too small to be effective clinically. The relationship between liver extract and folic acid is not yet clear.

Ascorbic Acid

(Cevitamic Acid)

Suboptimal intakes of ascorbic acid result in the development of clinical and pathologic phenomena to which the descriptive term scurvy has been applied.

Ascorbic acid has the following structural formula



All pure ascorbic acid that has been used in pharmaceutical products in recent years has been prepared synthetically. The international unit for ascorbic acid, which was formerly defined as the vitamin C activity of 0.1 cc. of lemon juice is now defined as the activity of 0.05 mg. of ascorbic acid. This is the quantity of ascorbic acid usually found in 0.1 cc. of lemon juice or orange juice.

in the diet, or in cases in which it is definitely known that there is interference with the absorption of an optimal amount.

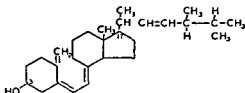
Advertising of ascorbic acid for such symptoms as failure to gain in weight or stoppage of growth, anorexia, anemia, infections, symptoms referable to the central nervous system or

administering it (or orange juice) in mixtures, or by any procedure which renders it ineffective

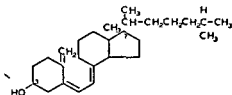
Vitamin D

The term "vitamin D" is applied to two or more substances which have a function in the proper utilization of calcium and phosphorus. Two forms of naturally occurring vitamin D have been isolated. One of these, vitamin D₂, or calciferol, is obtained in pure crystalline form as one of the products of the ultra-violet irradiation of ergosterol, the other, vitamin D₃, can be prepared in the same manner from 7-dehydro cholesterol. Antirachitic activation of these compounds can also be accomplished by electronic bombardment. The two forms of vitamin D, as well as some of the other products of irradiated ergosterol, possess antirachitic potency. They also tend to elevate the level of serum calcium, an effect which varies, however, with the different substances and which does not parallel the antirachitic effect.

Vitamin D₂ has the following structural formula



Activated 7-dehydro-cholesterol (vitamin D₃) has the following structural formula



Some reports have appeared claiming clinical improvement in chronic arthritis and in certain allergic disorders as a result of

the use of massive doses of vitamin D. Critical examination of these reports reveals little to warrant the belief that the clinical effects claimed are specific. There is suggestive clinical evidence that the use of massive doses of vitamin D may cause improvement in some cases of psoriasis, but the effect is not yet well enough established to justify a claim for such use. The Council believes that further studies should be conducted, but, because of the possible toxic effects of large doses of vitamin D, it is necessary that such studies should be made only in clinics where close supervision is possible. The Council also holds there is not sufficient evidence to warrant the acceptance of viosterol preparations of high potency for use in the treatment of arthritis.

Another suggested use of massive doses of vitamin D is in the

careful observation for signs of toxicity. Some investigators recommend the urine daily for calcium while the maintenance dose is less frequent examination is necessary. After the dose is established weekly examination, using the Sulkowitch test for excessive excretion of calcium, is sufficient. The blood should be examined weekly or oftener to avoid a rise of calcium above 12 mg. per hundred cubic centimeters if the dosage exceeds 20,000 units daily for the infant or 50,000 for the child and

the established procedure to state of closely. ved from of ergosterol and cholesterol are effective in result is achieved in part bones but also by an increased absorption of calcium; only Vitamin D₂ (calciferol) and dihydrotachysterol have received extensive clinical trials. Either of these substances may be administered by mouth over considerable periods of time and with reasonable safety provided the serum calcium is not permitted to rise above normal levels. There appears to be no development of tolerance.

Vitamin D₂ (calciferol) and dihydrotachysterol have similar effects in comparable doses, and it has not been shown that one is superior to the other in the management of hypoparathyroid-

ism. During their use frequent determinations of serum calcium are desirable, the Sulkowitch test, by which the excretion of calcium into the urine is observed is helpful and is so simple that it may be performed by the patient. Its routine use during treatment will reduce the number of necessary determinations of serum calcium.

Treatment of parathyroid insufficiency is commonly initiated with relatively large doses of the activated sterols, followed by smaller maintenance doses. The management of acute tetany and

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substances necessary for daily maintenance varies greatly in individual cases but averages between 0.6 and 1.0 mg. of pure dihydrotachysterol or 3.0 to 5.0 mg. (133,333 to 200,000 international units) of vitamin D.

Allowable Claims—1 Vitamin D is recognized as a specific in the treatment of infantile rickets, spasmophilia (infantile tetany) and osteomalacia diseases which are manifestations of abnormal calcium and phosphorus metabolism. Vitamin D is valuable in the prevention as well as in the curative treatment of these diseases. Complications such as renal insufficiency or glandular malfunction may preclude normal response to vitamin D therapy. During acute infections, especially of the gastrointestinal tract, vitamin D may prove ineffective because poorly absorbed.

2 Direct exposure of the skin to ultraviolet rays from vita-
gnize
-ficial

3 There is clinical evidence to justify the statement that vitamin D plays an important role in tooth formation. Likewise experimental evidence justifies the statement that vitamin D is a beneficial factor in preventing and arresting dental caries when the intake of calcium and phosphorus is liberal and the diet is adequate with respect to other nutrients. Claims should not state or imply that vitamin D is the only important factor in caries prevention or arrest.

4 Animal experimentation has shown that correction of an inadequate intake of vitamin D results in the more economical

man is not entirely apparent because of the lack of adequate clinical evidence showing the availability of different forms of calcium and phosphorus, but it may be stated that vitamin D has a favorable influence on calcium and phosphorus metabolism.

5 Because of its effect upon the level of serum calcium, vitamin D has been used in correcting the hypocalcemia of para

thyroid tetany. Satisfactory effects may be obtained with sufficient doses either of vitamin D₂ (calciferol) or of dihydro-tachysterol, a derivative of one of the products resulting from the irradiation of ergosterol. When vitamin D preparations are employed for the correction of hypocalcemia, patients must be under constant observation since the elevation of serum calcium above normal levels may be accompanied by serious or even fatal effects.

6. Clinical evidence does not warrant the claim that massive doses of vitamin D are of benefit in chronic arthritis, in allergic disorders, or in psoriasis. If representations are made for use of massive doses of vitamin D in the treatment of refractory rickets they must be accompanied by adequate precautions with respect to the danger of toxic effects and how they can be avoided as indicated in the paragraph immediately preceding the allowable claims for vitamin D.

Vitamin E

In 1925 it was demonstrated conclusively that vitamin E must be included in the diet of the rat to insure successful reproduction. There are at least three naturally-occurring compounds which have vitamin E activity: alpha, beta and gamma tocopherol. There have been comparatively few clinical studies dealing with the role of vitamin E in human physiology and they have not led to very definite conclusions. There seems to be agreement that the vitamin is of no value in the treatment of sterility. There are indications that it may be of value in the treatment of habitual abortion but further studies are necessary to clarify the picture.

Recently there has been renewed interest with respect to vitamin E owing to reports that administration of alpha tocopherol and other preparations of vitamin E have produced beneficial results in the treatment of some cases of degenerative diseases such as amyotrophic lateral sclerosis. This is not substantiated in any way by recent clinical evidence.

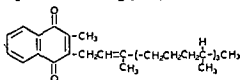
Vitamin K

Vitamin K was discovered and named by Dam of Copenhagen in 1935 when he observed in newly hatched chicks a fatal hemorrhagic diathesis which could be cured or prevented by the administration of a nonsteroidifiable substance.

physiologic properties and they are referred to as vitamin K₁ and vitamin K₂. Their empirical formulas are as follows:



Vitamin K₁ has the following structural formula:



Recently synthesized some being K₂, and some as vitamin K analogues

The Council has recognized the term 'menadione' for the compound 2-methyl-1,4-naphthoquinone. Menadione has the following structural formula:



There is now adequate deficiency in the blood of man the absorption of vitamin K, including vitamin K₁, are not obstructed, and synthesis of occur unless vitamin K is to administer bile salts with vitamin K when prothrombin deficiency is due to bile obstruction and the vitamin is given orally. While bile salts are necessary for the absorption of most of

significance of this observation is not as yet apparent.

Allowable Claims.—Vitamin K, both in its crude form and in certain related naphthoquinones with analogous antihemorrhagic activity, seems to have a specific effect on prothrombin deficiency occurring under certain sets of circumstances.

1 In primary dietary deficiency of vitamin K which, while admittedly rare, does exist.

2 In obstructive jaundice, in which vitamin K has proved to have an extraordinary protective effect against hemorrhagic diathesis.

3 The hemorrhagic state associated with primary hepatic disease is controlled in part, but not entirely, by vitamin K and

by the naphthoquinones with analogous activity. The difficulty seems to lie in the fact that the liver cannot utilize the material in the formation of prothrombin, except to a limited degree.

4. The hemorrhagic states, which exist in connection with certain intestinal diseases such as ulcerative colitis, sprue and celiac disease, characterized by a discontinuity of the intestinal mucous membrane and a consequent loss of the absorptive surface, are also affected.

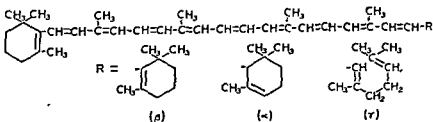
5. In the treatment of the physiological hypoprothrombinemia of the newborn, which exists during the first week of life, the vitamin and its analogues seem to be specific. It seems now fairly well established that the vitamin itself or the naphthoquinones, when administered parenterally to a woman during labor, in amounts as small as $\frac{1}{2}$ to 2 mg., insures that the newborn infant will have a normal amount of prothrombin in the circulating blood. These doses can also be given parenterally to the newborn infant and will produce the same effect.

VITAMIN PREPARATIONS

Vitamin A Preparations

Vitamin A is found in fish liver oils. The provitamin A, carotene, gives the effects of vitamin A when ingested.

CAROTENE.—Pro-Vitamin A.—A hydrocarbon having the empiric formula $C_{40}H_{56}$ which occurs in three isomeric forms referred to respectively as alpha, beta and gamma carotene. The structural formulas of these compounds may be represented as follows:



The alpha form is optically active and the others are not. The beta form appears to predominate in nature, and the gamma is found in the smallest quantities, but usually a mixture of the different forms occurs. The crystals are readily oxidized. They should be kept in a vacuum or in an inert gas in the dark at a low temperature. The International unit for vitamin A adopted by the International Union of Pure and Applied Chemistry is defined as the activity of 0.6 microgram of pure beta-carotene. The Council has reached the following decision with respect to the use of the term "Pro-vitamin

A as a synonym for carotene (1) that the term 'A Pro vitamin A' be used only when the product is a mixture of carotene and vitamin A.

is used on the label of any accepted product it appear in brackets after the Council name with a statement of the vitamin A potency of the product

Actions and Uses—It appears that at least a portion of the carotene ingested is converted in the liver into vitamin A. Carotene therefore has actions similar to those of vitamin A. As carotene may be a mixture of the alpha, beta and gamma forms its relative efficiency may vary according to the ratio of these components. Evidence is not available on which to base the exact conversion factor of carotene in terms of clinical vitamin A effect. Much depends on the conditions for absorption of pigment. Carotene prevents its absorption and should not be administered together with preparations of carotene. In view of the fact that cases of carotenemia have arisen from overdosage the Council

Dosage—See statement under vitamin A and D Preparations. Carotene is generally administered in the form of carotene dissolved in an oily solution.

WYETH INCORPORATED
Solution Carotene Concentrate in Oil 50 cc bottle. A solution containing carotene in cottonseed oil. It is biologically assayed to have in each gram a vitamin A potency of not less than 7,500 units U. S. P. Accompanied by a dropper designed to deliver 25 drops to the cubic centimeter.

Capsules Carotene Concentrate in Oil Each capsule contains an amount of carotene equivalent to 5,000 U. S. P. units of vitamin A.

Oleovitamin A U. S. P.—Natural Vitamin A in Oil. It is a solution of vitamin A in cottonseed oil. It is biologically assayed to have in each gram a vitamin A potency of not less than 7,500 units U. S. P. Accompanied by a dropper designed to deliver 25 drops to the cubic centimeter.

Oleovitamin A Capsules Each capsule contains an amount of vitamin A equivalent to 5,000 U. S. P. units of vitamin A.

For description and standards see the U. S. Pharmacopeia under Oleovitamin A and Oleovitamin A Capsules.

Actions, Uses and Dosage See statement under vitamin A and D preparations.

ABBOTT LABORATORIES

Capsules Oleo Vitamin A: Each capsule contains 25,000 U. S. P. units of vitamin A derived from natural fish liver oils

AMERICAN PHARMACEUTICAL Co., Inc.

Capsules Oleovitamin A: Each capsule contains 25,000 U. S. P. units of vitamin A derived from fish liver oils.

INTERNATIONAL VITAMIN DIVISION, IVES-CAMERON COMPANY

Capsules Oleo Vitamin A: Each capsule contains 25,000 U. S. P. units of vitamin A derived from fish liver oils.

PREMO PHARMACEUTICAL LABORATORIES, INC.

Capsules Vitamin A: Each capsule contains 25,000 U. S. P. units of vitamin A derived from natural fish liver oils.

WALKER VITAMIN PRODUCTS, INC.

Capsules Oleo Vitamin A: Each capsule contains 25,000 U. S. P. units of vitamin A derived from fish liver oils.

WHITE LABORATORIES, INC.

Capsules Oleo-Blend Vitamin A: Each capsule contains 25,000 U. S. P. units of vitamin A derived from fish liver oils.

Vitamin B Complex Preparations

The Council will consider for acceptance the following types of preparations containing mixtures of the components of the vitamin B complex.

(1) Mixtures of pure thiamine, riboflavin and nicotinic acid providing in the recommended daily intake: 1 milligram thiamine, 1.5 to 2 milligrams riboflavin, 10 milligrams nicotinic acid, or simple multiples thereof.

(2) Dried yeast U. S. P. containing the following minimum content per gram: 1 milligram thiamine, 1.5 milligrams riboflavin, and 0.250 milligram nicotinic acid.

(3) Dried yeast U. S. P. to which has been added riboflavin and nicotinic acid in such quantities that for each milligram of thiamine contained in the finished product there are present 1.5 to 2 milligrams of riboflavin and 10 milligrams of nicotinic acid.

(4) A concentrate of the vitamin B complex from brewer's yeast as described under (2), and providing in the recommended daily intake: 1 milligram of thiamine (or a simple multiple thereof) and corresponding proportions of other known vitamins of yeast.

(5) A concentrate of the vitamin B complex from liver containing in each gram not less than 0.25 milligram of riboflavin.

(6) A concentrate of the vitamin B complex from brewer's yeast fortified with riboflavin and nicotinic acid and providing

in the recommended daily intake 1 milligram thiamine, 15 to 2 milligrams riboflavin, and 10 milligrams nicotinic acid, or simple multiples thereof

simple multiples thereof

DRIED YEAST-U. S. P.—Dry Yeast—"Dried Yeast consists of the dry cells of any suitable strain of *Saccharomyces cerevisiae* Meyen (Fam. *Saccharomycetaceae*) Dried Yeast may be obtained as a by-product from the brewing of beer which has been made from an extract from cereal grain and hops. The yeast cells are washed free of beer and dried, and may or may not be debittered. These yeasts are commonly known, respectively, as 'Brewer's Dried Yeast' and 'Debittered Brewer's Dried Yeast'. Dried Yeast may also be obtained by growing suitable strains of yeast, using media other than those required for the production of beer, and under appropriate environmental conditions. The yeast thus obtained is commonly known as 'Primary Dried Yeast'.

"Dried Yeast contains not less than 40 per cent of protein and, in each Gm, the equivalent of not less than 0.12 mg of thiamine hydrochloride, 0.04 mg of riboflavin and 0.25 mg of nicotinic acid"—U. S. P.

For further description and standards see the U. S. Pharmacopeia under Dried Yeast and Dried Yeast Tablets.

Actions and Uses—Yeast extract containing vitamin B complex is proposed for prophylaxis and treatment of conditions arising from deficiency of the vitamin B complex in the diet.

Dosage—Infants 2 cc. to 4 cc. of the liquid preparation daily, children 4 cc. to 12 cc. of the liquid preparation, adults 12 cc. to 24 cc. of the liquid preparation.

ABBOTT LABORATORIES

Tablets Brewer's Yeast, 0.4 Gm (Fortified with Riboflavin and Nicotinic Acid) Each tablet contains Abbott's Brewer's Yeast Powder Fortified with Riboflavin and Nicotinic Acid 0.4 Gm, providing in each tablet vitamin B₁ 0.06 mg, riboflavin 0.12 mg, nicotinic acid 0.6 mg. Average daily dose, as a supplement to the diet for children 6 to 12 years old, 6 tablets, older children and adults 9 tablets, therapeutic doses must be determined for each patient.

Tablets Brewer's Yeast, 0.5 Gm (Fortified with Riboflavin and Nicotinic Acid) Each tablet contains 0.5 Gm of dried brewer's yeast (*Saccharomyces cerevisiae*), debitterized fortified with crystalline riboflavin and nicotinic acid to contain in each tablet vitamin B₁, 0.1 mg, riboflavin 0.2 mg and nicotinic acid 1 mg. Prophylactic dose for adults 10 tablets daily, therapeutic doses must be determined for each patient.

Preparation.—

Abbott's brewer's yeast tablets are prepared from a selected strain of *Saccharomyces cerevisiae* especially cultured. The yeast cells are washed and dried, the dry powder containing approximately 5 per cent of moisture, and compressed into tablets.

The vitamin B₁ content of the tablets is determined by comparison with the international standard by the modified Smith rat curative method. The vitamin G content is determined by the Sherman-Bourquin method.

KINNEY AND COMPANY

Kinney's Yeast Extract (Liquid): 125 cc. bottles. Biologically assayed to contain in each 1 cc. the equivalent of not less than 0.075 mg. (25 I. U.) of thiamine hydrochloride and 0.025 mg. (10 Sherman-Bourquin units) of riboflavin. Preserved with glycerin and simple syrup.

Preparation.—

Kinney's yeast extract containing vitamin B complex is prepared by extracting specially cultured dried brewer's yeast in an aqueous medium under proper conditions of pH control. The extract is concentrated and clarified. It is then preserved in liquid form by the addition of an equal volume of a mixture of equal parts of glycerin and simple syrup.

MCNEIL LABORATORIES, INC.

Tablets Brewer's Yeast: 0.3 Gm. Each tablet contains brewer's yeast 0.32 Gm., providing thiamine hydrochloride 0.167 mg. (55.5 U. S. P. units), riboflavin 0.023 mg. and niacin 0.195 mg.

Preparation.—

Dried Brewer's Yeast—U. S. P.—Granulated with a mixture of calcium carbonate, starch, sodium chloride, dried malt syrup, saccharin, vanillin, oil of chocolate and tale. The mixture is compressed into tablets.

MEAD JOHNSON AND COMPANY

Brewer's Yeast (Powder): 28.35 Gm. (11 level teaspoons or 3 level tablespoons). Each gram contains not less than thiamine (vitamin B₁) 0.18 mg., riboflavin (vitamin G) 0.06 mg. and niacin 0.4 mg., together with other factors of the vitamin B complex commonly occurring in brewer's yeast. Dosage for infants, $\frac{1}{2}$ to 1 level teaspoon in the milk formula. For children 1 to 6, 1 to 2 level teaspoons in milk or tomato juice. For use as a supplement in the treatment of deficiencies of various factors of the vitamin B complex, dosage will depend on the type of specific vitamin therapy employed, the severity of the condition and the individual patient; in general, 2 to 4 level teaspoons daily. For supplementary use with specific vitamin therapy in ariboflavinosis and pellagra, 7 or more level teaspoons daily.

Tablets Brewer's Yeast: 0.4 Gm. Each tablet contains 0.4 Gm. dehydrated brewer's yeast supplying thiamine hydrochloride 0.06 mg., riboflavin 0.02 mg. and 0.15 mg. niacin together with other factors of the vitamin B complex commonly occurring in brewer's yeast. Dosage for children, 6 to 10 tablets daily, for adults, 10 to 12 daily, for pregnancy and lactation, 12 to 20 tablets daily. For use as a supplement in the treatment of deficiencies of various factors of the vitamin B complex, dosage will depend on the type of specific vitamin therapy employed, the severity of the condition and the individual patient, in general, 8 to 20 tablets daily. For supplementary use with specific vitamin therapy in ariboflavinosis and pellagra, 35 or more tablets daily.

Preparation—

Mead's brewer's yeast powder is a dried nonviable strain of *Saccharomyces cerevisiae* cultured especially for its vitamin content. It is readily suspended in water, milk, tomato juice or other suitable fluids.

E. R. SQUIBB & SONS

Tablets Brewer's Yeast: 0.4 Gm. Each tablet contains 0.4 Gm. dehydrated brewer's yeast supplying thiamine hydrochloride 0.06 mg., riboflavin 0.03 mg., and niacin 0.15 mg.

VITAMIN B COMPLEX SYRUP—A syrup prepared from a concentrated extract of dried brewer's yeast and an extract of corn processed with *Clostridium acetobutylicum*, with inverted cane sugar 40 per cent w/v and natural flavoring.

*Actions and Uses—*Proposed for prophylaxis and treatment of conditions arising from deficiency of the vitamin B complex.

MARVIN R. THOMPSON, INC.

Syrup Vitamin B Complex: Each 5 cc. contains thiamine hydrochloride 15 mg., riboflavin 10 mg., pyridoxine hydrochloride 0.5 mg., niacin and nicotinamide 70 mg. with other vitamin B complex factors as extracted from 10 Gm. of dried brewer's yeast.

V1 Co Products Co.

Syrup Vitamin B Complex: Each 5 cc. contains thiamine hydrochloride 15 mg., riboflavin 10 mg., pyridoxine hydrochloride 0.5 mg. and nicotinic acid 70 mg., with other vitamin B complex factors as extracted from 10 Gm. of dried brewer's yeast.

U. S. patent 2,193,876 (March 19, 1940; expires 1957).

Thiamine Preparations

U. S. P.

—U. S. P.—Betabion

B₁ hydrochloride—V₁

ours contains not less

U. S. P.

U. S. Pharmacopeia

Thiamine Hydrochloride, Thiamine Hydrochloride Injection and Thiamine Hydrochloride Tablets

Acceptance of tablets thiamine hydrochloride will be limited to $\frac{1}{2}$, 1, 3, 5 and 10 mg. of thiamine hydrochloride per tablet, and the acceptance of solutions thiamine hydrochloride for parenteral use will be limited to 1, 5, and 10 mg. thiamine hydrochloride per cc. No dosage form in containers larger than 10 cc. size will be considered for acceptance.

Actions and Uses.—See article, Thiamine.

Dosage.—The minimum daily requirement of thiamine for an adult appears to be approximately 1 mg., and the optimum intake is said to lie between 1.5 and 2.5 mg. For the child, the optimum intake may be calculated from the caloric requirement, by allowing at least 0.03 milligram for each 100 calories. In the well-balanced diet the thiamine requirement should be obtained from the food.

When pharmaceutical preparations of thiamine hydrochloride are prescribed, the minimum daily prophylactic dosage for the infant should not be less than 0.15 mg. and for the adult should not be less than 1 mg. There appears to be no satisfactory evidence that prophylactic dosages in excess of 0.5 mg. for the infant and 3 mg. for the adult are indicated. Evidence on which to base dosages in the treatment of acute deficiencies is meager. There are indications that doses of the order of 10 to 50 mg. in certain instances. Thiamine is rapidly absorbed and indications for parenteral administration is intravenous administration is indicated. There is evidence indicating that injections of large dosages of solutions of high potency may cause anaphylactic shock.

ABBOTT LABORATORIES

Tablets Thiamine Hydrochloride: 3 mg., 5 mg. and 10 mg.

Solution Thiamine Hydrochloride: 10 mg. per cc. 10 cc. bottle. Each cc. contains thiamine hydrochloride 10 mg., sodium chloride 57 mg. and benzyl alcohol 9 mg. in chemically pure water. This preparation is for parenteral administration.

AMERICAN PHARMACEUTICAL CO., INC.

Tablets Thiamine Hydrochloride: 1 mg., 5 mg. and 10 mg.

GEORGE A. BREON & COMPANY, INC.

Solution Thiamine Hydrochloride: 10 mg. per cc. 10 cc. vial. Contains sodium chloride 7.5 mg. per cc. Preserved with chlorobutanol 0.5 per cent.

Tablets Thiamine Hydrochloride: 10 mg.

BRISTOL LABORATORIES, INC.

Solution Thiamine Hydrochloride: 10 mg. per cc. 1 cc ampuls and 5 cc. vials. Each cc. contains 10 mg. of crystalline vitamin B₁ hydrochloride, 5 mg. of chlorobutanol in double distilled water.

BURROUGHS WELLCOME & Co INC.

Tabloid Thiamine Hydrochloride 5 mg and 10 mg
U S trademark 76 731

COLE CHEMICAL COMPANY

Solution Thiamine Hydrochloride 15 mg and 30 mg per
30 cc. bottles and 475 cc and 378 liter bottles

Tablets Thiamine Hydrochloride 1 mg 3 mg and 5 mg

THE DRUG PRODUCTS Co INC.

Pulvoids Thiamine Hydrochloride 1 mg 3 mg

Solution Thiamine Hydrochloride 10 mg per cc. 1 cc.
ampul hypodermics

Solution Thiamine Hydrochloride 10 mg per cc 10 cc.
hypodermic vials Preserved with chlorobutanol 0.5 per cent.

R. E. DWIGHT & COMPANY

Tablets Thiamine Hydrochloride 5 mg and 10 mg

ENDO PRODUCTS INC.

Solution Thiamine Hydrochloride 10 mg per cc 1 cc
ampuls and 10 cc vials Preserved with chlorobutanol 0.5 per
cent

Tablets Thiamine Hydrochloride 1 mg 3 mg and 5 mg

FLINT EATON & COMPANY

Solution Thiamine Hydrochloride 10 mg per cc 1 cc
ampuls

Tablets Thiamine Hydrochloride 1 mg 5 mg and 10 mg

THE HAPPOWER LABORATORY INC.

Tablets Thiamine Hydrochloride 10 mg

HORTON & CONVERSE

Tablets Thiamine Hydrochloride 1 mg 5 mg and 10 mg

INTERNATIONAL VITAMIN DIVISION Ives CAMFROV COMPANY,
INC.

Tablets Thiamine Hydrochloride 1 mg 3 mg 5 mg and
10 mg

KREMERS URBAN Co

Tablets Thiamine Hydrochloride 3 mg and 10 mg

LINCOLN LABORATORIES INC

Solution Thiamine Hydrochloride 10 mg per cc., 10 cc.
vials. Preserved with chlorobutanol 0.5 per cent

McKesson & Robbins INC.

Tablets Thiamine Hydrochloride 0.5 mg 1 mg and 3 mg

MERCK & Co., INC.

Betabion (*Powder*): 1 Gm bottle.

U. S. trademark 336,518.

Thiamine Hydrochloride (*Powder*).

THE WM. S. MERREL COMPANY

Tablets Thiamine Hydrochloride: 1 mg., 3 mg., 5 mg. and 10 mg.

E. S. MILLER LABORATORIES, INC.

Solution Thiamine Hydrochloride: 10 mg. per cc. 1 cc. ampuls.

Tablets Thiamine Hydrochloride: 5 mg. and 10 mg

NATIONAL DRUG COMPANY

Tablets Thiamine Hydrochloride: 1 mg.

WILLIAM H. RORER, INC.

Tablets Thiamine Hydrochloride: 1 mg. and 5 mg

SCHIEFFELIN & Co.

Tablets Thiamine Hydrochloride: 3 mg., 5 mg. and 10 mg.

CARROLL DUNHAM SMITH PHARMACAL COMPANY

Solution Thiamine Hydrochloride: 10 mg. per cc. 1 cc. ampuls. Each cc. contains thiamine hydrochloride 10 mg. in isotonic solution of sodium chloride. Preserved with chlorobutanol 0.5 per cent.

Tablets Thiamine Hydrochloride: 5 mg. and 10 mg.

SMITH-DORSEY COMPANY

Solution Thiamine Hydrochloride: 10 mg. per cc. 10 cc. vials. Each cc. contains thiamine hydrochloride in an isotonic solution of sodium chloride. Preserved with chlorobutanol 0.5 per cent.

Tablets Thiamine Hydrochloride: 5 mg. and 10 mg.

E. R. SQUIBB & SONS

Tablets Thiamine Hydrochloride: 5 mg and 10 mg.

WINTHROP-STEARNs, INC.

Tablets Thiamine Hydrochloride: 5 mg. and 10 mg.

U. S. VITAMIN CORPORATION

Solution Thiamine Hydrochloride: 10 mg. per cc. 1 cc. ampuls and 5 cc. and 10 cc. vials Preserved with chlorobutanol 0.5 per cent.

Tablets Thiamine Hydrochloride: 5 mg. and 10 mg.

THE UPJOHN COMPANY

Solution Thiamine Hydrochloride 10 mg per cc 1 cc ampuls and 10 cc vials Preserved with chlorobutanol 0.5 per cent

Tablets Thiamine Hydrochloride 1 mg 3 mg 5 mg and 10 mg

THE VALE CHEMICAL CO., INC.

Tablets Thiamine Hydrochloride 1 mg 3 mg, 5 mg and 10 mg

WALKER VITAMIN PRODUCTS, INC.

Solution Thiamine Hydrochloride 0.3 mg per drop 15 cc. and 60 cc bottles For oral administration

Tablets Thiamine Hydrochloride 1 mg 3 mg, 5 mg and 10 mg

WARREN-TEED PRODUCTS COMPANY

Tablets Thiamine Hydrochloride 10 mg

WHITE LABORATORIES, INC.

Tablets Thiamine Hydrochloride 5 mg

WYETH, INCORPORATED

Tablets Thiamine Hydrochloride 10 mg

MIXED VITAMIN B COMPONENTS

TRIASYN B-U. S. P.—Triasyn B Capsules and Tablets contain in each capsule or tablet not less than 2 mg of thiamine hydrochloride 3 mg of riboflavin and 20 mg of nicotinamide."
—U. S. P.

For description and standards see the U. S. Pharmacopoeia under Triasyn B Capsules and Triasyn B Tablets

Actions, Uses and Dosage.—For prophylaxis and treatment of conditions arising from deficiency of thiamine, riboflavin and nicotinic acid. See articles on the various vitamins concerned.

PREMO PHARMACEUTICAL LABORATORIES, INC.

Capsules Triasyn B. Each capsule contains 2 mg of thiamine hydrochloride, 3 mg of riboflavin and 20 mg of nicotinic acid amide.

Tablets Triasyn B. Each tablet contains 2 mg of thiamine hydrochloride, 3 mg of riboflavin and 20 mg of nicotinic acid amide.

RIBOFLAVIN PREPARATIONS

RIBOFLAVIN-U. S. P.—Lactoflavin. Vitamin B₂—Vitamin G

For description and standards see the U. S. Pharmacopeia under Riboflavin, Riboflavin Injection and Riboflavin Tablets

Acceptance of tablets riboflavin will be limited to 1, 2, 5 and 10 mg. of riboflavin per tablet and the acceptance of solutions riboflavin for parenteral use will be limited to 0.2 mg. Riboflavin per cc., except that special consideration will be given to solutions of higher concentrations that may be obtained by the use of other reagents.

Actions and Uses.—See article, Riboflavin.

Dosage.—The optimum intake of riboflavin for an infant appears to be approximately 1 mg. per day, and for an adult approximately 3 mg. per day. The requirement during pregnancy and lactation is higher. When riboflavin is used therapeutically the dosage varies from 2 to 10 mg. per day depending upon the severity of the deficiency. No side effects have been noticed following the administration of relatively large doses.

ABBOTT LABORATORIES

Capsules Riboflavin: 5 mg.

Tablets Riboflavin: 1 mg., 5 mg. and 10 mg.

AMERICAN PHARMACEUTICAL CO., INC.

Tablets Riboflavin: 1 mg. and 5 mg.

GEORGE A. BREON & COMPANY, INC.

Tablets Riboflavin: 5 mg.

ENDO PRODUCTS, INC.

Tablets Riboflavin: 5 mg.

THE HARROWER LABORATORY, INC.

Tablets Riboflavin: 5 mg.

INTERNATIONAL VITAMIN DIVISION, IVES-CAMERON COMPANY, INC.

Tablets Riboflavin: 1 mg., 2 mg. and 5 mg.

MERCK & CO., INC.

Riboflavin (*Powder*)

THE WM. S. MERRELL COMPANY

Tablets Riboflavin: 5 mg.

PREMO PHARMACEUTICAL LABORATORIES, INC.

Tablets Riboflavin: 1 mg., 2 mg., 5 mg. and 10 mg.

U. S. VITAMIN CORPORATION

Tablets Riboflavin: 1 mg. and 5 mg.

THE UPJOHN COMPANY

Tablets Riboflavin: 5 mg.

WALKER VITAMIN PRODUCTS INC.

Tablets Riboflavin 1 mg 5 mg and 10 mg

WARREN TEED PRODUCTS COMPANY

Tablets Riboflavin 1 mg

NICOTINIC ACID AND NICOTINAMIDE PREPARATIONS

NICOTINIC ACID U S P—Niacin—'When dried for 3 hours over sulfuric acid contains not less than 99.5 per cent of $C_6H_5O_2N$ U S P

For description and standards see the U S Pharmacopeia under Nicotinic Acid and Nicotinic Acid Tablets

Actions and Uses—See article, Nicotinic Acid and Nicotinamide

Dosage—The optimum intake of nicotinic acid has not been established with certainty. However for adults it seems to be of the order of 15 to 20 mg per day. The dose for therapeutic purposes varies considerably from person to person depending upon the severity of the deficiency and possibly upon other as

recommended

to 25-50
mg nicotinic

ABBOTT LABORATORIES

Tablets Nicotinic Acid 50 mg and 100 mg

AFRICAN PHARMACEUTICAL CO. INC.

Nicotinic Acid (Powder) 125 Gm bottles

Tablets Nicotinic Acid 25 mg., 50 mg and 100 mg

ENDO PRODUCTS INC.

Tablets Nicotinic Acid 50 mg and 100 mg

FLINT EATON & COMPANY

Tablets Nicotinic Acid 25 mg

INTERNATIONAL VITAMIN DIVISION Ives CAMERON COMPANY, INC.

Tablets Nicotinic Acid 25 mg 50 mg and 100 mg

MERCK & Co. INC.

Niacin (Powder)

THE WM. S. MERRELL COMPANY

Tablets Nicotinic Acid 50 mg

Tablets Nicotinic Acid Amide: 50 mg. and 100 mg.

THE VALE CHEMICAL CO., INC.

Tablets Nicotinamide: 50 mg.

WALKER VITAMIN PRODUCTS, INC.

Tablets Niacinamide: 25 mg., 50 mg. and 100 mg.

WARREN-TEED PRODUCTS COMPANY

Tablets Nicotinamide: 50 mg.

PYRIDOXINE PREPARATIONS

It may be isolated from natural sources or prepared synthetically from ethoxy-acetylacetone and cyanoacetamide.

For tests and standards, see Section B.

Actions and Uses.—The nutritive and therapeutic value of pyridoxine hydrochloride has not been definitely established. It has been accepted by the Council for purposes of standardization and experimentation only.

Dosage.—A dose of 5 to 10 mg. daily is suggested.

BREWER & CO., INC.

Solution Pyridoxine Hydrochloride: 50 mg. per cc., 10 cc. vials.

ENDO PRODUCTS, INC.

Solution Pyridoxine Hydrochloride: 25 mg. and 50 mg. per cc., 1 cc. ampuls and 50 mg. per cc., 10 cc. vials.

LAKESIDE LABORATORIES, INC.

Solution Pyridoxine Hydrochloride: 50 mg. per cc., 5 cc. vials.

Tablets Pyridoxine Hydrochloride: 20 mg.

MERCK & CO., INC.

Hexabione Hydrochloride (*Powder*): 100 mg. bottles.

U. S. trademark 377,657.

U. S. VITAMIN CORPORATION

Solution Pyridoxine Hydrochloride: 50 mg. per cc., 10 cc. vials. Preserved with chlorobutanol 0.5 per cent.

THE UNION COMPANY

Solution Pyridoxine Hydrochloride: 50 mg. per cc., 2 cc. ampuls.

Tablets Pyridoxine Hydrochloride: 10 mg.

Folic Acid Preparations

FOLIC ACID—Folvite (LEDERLE)—Pteroylglutamic acid—N [4- { [(2 amino 4 hydroxy 6 pteridyl)methyl]amino } benzoyl] glutamic acid

For tests and standards see Section B

Actions and Uses—Folic acid is effective in bringing about a response of the blood similar to that obtained with liver extract in pernicious anemia sprue and nutritional macrocytic anemia. It also controls the diarrhea in sprue, but probably does not prevent or cause improvement in the spinal cord lesions in pernicious anemia, these are helped by liver extract. Therefore folic acid should be used at this time only as an adjunct to liver therapy for the treatment of pernicious anemia.

Dosage—5 to 10 mg daily by mouth. (This is a preliminary estimate.) It may be administered by intramuscular injection but in ordinary cases there is no advantage.

ABBOTT LABORATORIES

Solution Folic Acid 15 mg per cc. 1 cc. ampuls. Each cc contains folic acid 15 mg and methylglucamine 24 mg as solubilizing agent.

Tablets Folic Acid 5 mg

AMERICAN PHARMACEUTICAL CO. INC.

Tablets Folic Acid 5 mg

KREMERS URBAN CO.

Tablets Folic Acid 5 mg

LEDERLE LABORATORIES DIVISION AMERICAN CYANAMID CO.

Elixir Folvite 5 mg per 4 cc. 125 cc. bottles

Tablets Folvite 5 mg

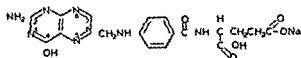
R. J. STRASENBURGH CO.

Tablets Folic Acid 5 mg

WALKER VITAMIN PRODUCTS INC.

Tablets Folic Acid 5 mg and 10 mg

SODIUM FOLATE—Sodium Folvite (LEDERLE)—Sodium pteroylglutamate. Sodium N [4- { [(2 amino 4 hydroxy 6 pteridyl)methyl]amino } benzoyl] glutamate. The structural formula for sodium folate may be represented as follows:



For tests and standards see Section B.

PREMO PHARMACEUTICAL LABORATORIES, INC.

Tablets Ascorbic Acid: 25 mg., 50 mg. and 100 mg.

SCHIEFFELIN & Co.

Tablets Ascorbic Acid: 25 mg., 50 mg. and 100 mg.

CARROLL DUNHAM SMITH PHARMACEUTICAL COMPANY

Tablets Ascorbic Acid: 100 mg.

SMITH-DORSEY COMPANY

Tablets Ascorbic Acid: 25 mg., 50 mg. and 100 mg.

E. R. SQUIBB & SONS

Tablets Ascorbic Acid: 25 mg., 50 mg. and 100 mg.

U. S. VITAMIN CORPORATION

Tablets Ascorbic Acid: 25 mg., 50 mg. and 100 mg.

THE UPJOHN COMPANY

Tablets Ascorbic Acid: 25 mg., 50 mg. and 100 mg.

WALKER VITAMIN PRODUCTS, INC.

Tablets Ascorbic Acid: 25 mg., 50 mg. and 100 mg.

Vitamin C Drops: 15 cc. bottles with dropper. Each cc. contains 150 mg. of ascorbic acid, 0.25 cc. of water and 0.003 cc. orange oil, three parts of propylene glycol to one of glycerine.

WARREN-TEED PRODUCTS COMPANY

Tablets Ascorbic Acid: 100 mg.

WINTHROP-STEARNS, INC.

Tablets Ascorbic Acid: 50 mg. and 100 mg.

WYETH, INCORPORATED

Tablets Ascorbic Acid: 100 mg.

SODIUM ASCORBATE INJECTION-U. S. P.

"A sterile solution of sodium ascorbate ($C_6H_7NaO_6$) in water for injection. It contains not less than 95 per cent and not more than 115 per cent of the labeled amount of Ascorbic Acid $C_6H_8O_6$." U. S. P.

For description and standards see the U. S. Pharmacopoeia under Sodium Ascorbate Injection.

Actions and Uses.—Sodium ascorbate possesses the activity of ascorbic acid and is preferred when parenteral therapy is indicated.

Dosage.—Same as for ascorbic acid.

HARRY BIOLOGICAL LABORATORY, DIVISION OF HARRY LABORATORIES, INC.

Solution Sodium Ascorbate: 50 mg. per cc., 2 cc. ampule.

Each 2 cc. contains sodium ascorbate equivalent to 100 mg of ascorbic acid.

GEORGE A. BREON & COMPANY, INC.

Solution Sodium Ascorbate: 50 mg. per cc., 2 cc ampuls. Each 2 cc. contains sodium ascorbate equivalent to 100 mg (2,000 international units) ascorbic acid in sterile aqueous solution

Solution Sodium Ascorbate: 50 mg per cc., 10 cc ampuls

THE CENTRAL PHARMACAL CO

Solution Sodium Ascorbate: 100 mg per cc., 10 cc. vials

ENDO PRODUCTS, INC.

Solution Sodium Ascorbate: 50 mg per cc., 2 cc ampuls. Each cc. contains sodium ascorbate equivalent to 50 mg of ascorbic acid, stabilized with the equivalent of 0.08 per cent sulfurous acid.

Solution Sodium Ascorbate: 50 mg per cc., 5 cc and 10 cc ampuls. Each cc contains sodium ascorbate equivalent to 100 mg of ascorbic acid, stabilized with the equivalent of 0.08 per cent sulfurous acid

KREMERS-URBAN COMPANY

Solution Sodium Ascorbate: 100 mg per 2 cc., 2 cc. ampuls

LINCOLN LABORATORIES, INC.

Solution Sodium Ascorbate: 100 mg. per cc., 2 cc. and 5 cc. ampuls

THE WM S MERRELL CO

Solution Sodium Ascorbate: 100 mg per cc., 2 cc. ampuls

WILLIAM H ROBER

Solution Sodium Ascorbate: 100 mg per cc., 1 cc., 5 cc. and 10 cc. ampuls. Each cc. contains sodium ascorbate equivalent to 100 mg (2,000 international units) ascorbic acid and thiourea 0.01 per cent in sterile aqueous solution

Vitamin D Preparations or Preparations Giving Vitamin D Effect

COD LIVER OIL WITH VIOSTEROL (See under Vitamins A and D Preparations)

HALIBUT LIVER OIL WITH VIOSTEROL (See under Vitamins A and D Preparations).

SYNTHETIC OLEOVITAMIN D-U. S. P.—Viosterol in Oil. (Applying only to Activated Ergosterol in Oil) Irradiated Ergosterol in Oil—"A solution of activated ergos-

terol, or activated 7-dehydrocholesterol, in an edible vegetable oil. Synthetic Oleovitamin D contains in each Gm. not less than 10,000 U. S. P. units of vitamin D.

Synthetic Oleovitamin D must be labeled to indicate whether it contains activated ergosterol (*Vitamin D₂ or Viosterol*) or whether it contains activated 7-dehydrocholesterol (*vitamin D₃*). U. S. P. Preparations listed under the title, Viosterol in Oil, contain activated ergosterol.

For description and standards see the U. S. Pharmacopeia under Synthetic Oleovitamin D.

Actions and Uses.—See article, Vitamin D.

Dosage.—Daily prophylactic dose for the average infant, 5 drops (approximately 0.1 cc.); for the premature and rapidly growing infant, 15 drops (0.31 cc.); daily curative dose, 15 to 20 drops (0.31 to 0.41 cc.); in severe cases, doses in excess of 20 drops may be given. The marketed preparations are accompanied by a standard dropper designed to deliver 3 drops to the minim.

Preparation.—

Viosterol in Oil is prepared by either of the following methods:

(a) Irradiation of a solution of purified ergosterol by ultraviolet rays under a determined distance and intensity for a definite length of time, under reflux in an inert atmosphere. After irradiation the solution is concentrated and the majority of the unchanged ergosterol is removed. The remaining solvent is distilled in an inert atmosphere and the irradiated ergosterol is dissolved in a known weight of vegetable oil. The resulting oil solution is adjusted by admixture of a bland vegetable oil so that the final product when assayed by the U. S. P. method has a vitamin D potency of not less than 10,000 U. S. P. units per Gm.

U. S. patents 1,680,818 (August 14, 1928; expired) and 1,871,136 (August 9, 1932; expires 1949) by license of the Wisconsin Alumni Research Foundation.

(b) Activation of purified ergosterol by low velocity electrons, after which the activated ergosterol is separated and dissolved in vegetable oil. The resulting solution is adjusted by admixture of a bland vegetable oil so that the final product when assayed by the U. S. P. method has a vitamin D potency of not less than 10,000 U. S. P. units per Gm.

Manufactured by General Mills, Inc., Special Commodities Division, under license agreement with E. I. du Pont de Nemours & Company. U. S. patent 2,117,100 (May 10, 1938; expires 1955).

ABBOTT LABORATORIES

Solution Viosterol in Oil: 20 cc. and 50 cc. bottles in sesame oil.

AMERICAN PHARMACEUTICAL CO., INC.

Solution Viosterol in Oil: 10 cc. and 50 cc. bottles in vegetable oil.

INTERNATIONAL VITAMIN DIVISION, IVES-CAMERON COMPANY, INC.

Solution Viosterol in Oil: 10 cc. and 60 cc. bottles in neutral vegetable oil.

McKesson & Robbins, Inc.

Solution Viosterol in Oil: 10 cc. and 60 cc. bottles in neutral vegetable oil

Mead Johnson & Company

Solution Viosterol in Oil 10 cc. and 50 cc. bottles in corn oil

Parker, Davis & Company

Solution Viosterol in Oil 5 cc. and 50 cc. bottles in corn oil

E. R. Squibb & Sons

Solution Viosterol in Oil 5 cc., 20 cc. and 50 cc. bottles in corn oil.

VITAMIN D₂—Drisdol (WINTHROP VITAMINS)—9,10 Ergostatriene-(18, 10, 5, 6, 7, 8, 22, 23) of 3:1 or structural formula see the article on Vitamin D

Vitamin D₂ may be prepared by ultraviolet irradiation of ergosterol in a suitable solvent or by electronic bombardment of the compound. It is not identical with the vitamin D which predominates in fish liver oils and which is called vitamin D₃. A method of preparation of vitamin D₂ is given in Addendum 1936 to the British Pharmacopoeia, 1932, page 20. The crystals have a potency of 40 units of vitamin D (U. S. P.) per microgram. (1) or methods of assay see U. S. P. XIII, p. 723.)

For tests and standards, see Section B.

Actions and Uses—See article for vitamin D

WINTHROP STEARNS, INC.

Capsules Drisdol Concentrated Solution in Oil: 5 minims. Each capsule contains 1.25 mg. of Drisdol and has a potency of 50,000 units of vitamin D (U. S. P.).

Solution Drisdol in Propylene Glycol: 5 cc., 10 cc. and 50 cc. bottles. Each 1 cc. contains 0.25 mg. of drisdol and has a

potency of 250 U. S. P. units of vitamin D per drop. The product is marketed with a special dropper delivering 250 U. S. P. units of vitamin D per drop.

4 drops daily for the average infant, and up to 15 drops daily for the premature or rapidly growing infant. Daily curative dose 15 to 20 drops. The product is marketed with a special dropper delivering 250 U. S. P. units of vitamin D per drop.

U. S. patent 1,902,785 (March 21, 1933, expires 1950) and 2,030,792 (Feb. 11, 1936, expires 1953) and by license of the Wisconsin Alumni Research Foundation under U. S. patents 1,850,818 (Aug. 14, 1928; expired) and 1,873,136 (Aug. 9, 1932, expires 1949) U. S. trademark 33,661.

Vitamins A and D Preparations

CONCENTRATED OLEOVITAMIN A AND D.

U. S. P.—"Fish liver oil, or fish liver oil diluted with an edible vegetable oil, or a solution of Vitamin A and D concentrates in fish liver oil or in an edible vegetable oil. The Vitamin A obtained from natural (animal) sources and the Vitamin D may be obtained from natural (animal) sources or may be synthetic oleovitamin D. Concentrated Oleovitamin A and D contains in each gram S. P. than

For description and standards see the U. S. Pharmacopeia under Concentrated Oleovitamin A and D and Concentrated Oleovitamin A and D Capsules.

Actions, Uses and Dosage.—See under Vitamin A and D preparations.

McKesson & Robbins, Inc.

Concentrated Oleo Vitamins A and D: 6 cc. vials. A concentrate of vitamins A and D prepared from cod liver oil, the concentrate containing not less than 60,000 U. S. P. units of vitamin A and not less than 10,000 U. S. P. units of vitamin D per gram.

WALKER VITAMIN PRODUCTS, INC.

Drops Concentrated Oleo Vitamin A-D: Each gram contains not less than 62,500 U. S. P. units of vitamin A and not less than 10,000 U. S. P. units of vitamin D. Natural esters of vitamin A (distilled from fish liver and vegetable oils) plus activated ergosterol in refined corn oil. Flavored with cinnamon.

BURBOT LIVER OIL.—The oil extracted from the liver of the Burbot assayed to have
A (U. S. P.) 1
D (U. S. P.) per gram.

For tests and standards, see Section B.

Actions and Uses.—Same as those of cod liver oil. See article *Vitamins A and D Preparations*.

by
sig

BURBOT LIVER PRODUCTS Co

Burbot Liver Oil (Rowell): 60 cc. and 240 cc. bottles.

Capsules Burbot Liver Oil (Rowell): 0.52 cc. minims, adjusted to have a potency of not less than 2,215 units of vitamin A (U. S. P.) and 315 units of vitamin D (U. S. P.) per capsule

COD LIVER OIL-U. S. P.—"The partially destearinated fixed oil obtained from fresh livers of *Gadus morrhua* Linné and

other species of the family *Gadidae* Cod Liver Oil contains in each Gm. at least 850 U S P units of Vitamin A and at least 85 U S P Units of Vitamin D Cod Liver Oil may be flavored by the addition of not more than 1 per cent of any one or any mixture of flavoring substances recognized in the U S Pharmacopeia ' U S P

For description and standards see the U S Pharmacopeia under Cod Liver Oil.

Actions, Uses and Dosage—See article Vitamins A and D Preparations

COD LIVER OIL WITH VIOSTEROL — Viosterol dissolved in cod liver oil to adjust it to the potency of not less than 850 units (U S P) of vitamin A per Gm., 360 units (U S P) of vitamin D per Gm

Actions and Uses—See general article Viosterol Cod liver oil with viosterol is proposed for use in conditions in which it is desired to supplement the administration of vitamin A with that of a relatively large amount of vitamin D

Dosage—For infants and young children 25 to 33 cc. daily for adults and in severe cases doses up to 7 cc. or more are given.

Preparation—

Cod liver oil with viosterol is prepared by addition of irradiated ergosterol to cod liver oil in such proportion that the finished product will have a potency of not less than 850 units (U S P) of vitamin A per Gm. and not less than 360 units (U S P) of vitamin D per Gm.

MEAD JOHNSON & COMPANY

Cod Liver Oil with Viosterol 118 cc. and 473 cc. bottles
Each 1 Gm. has a potency of not less than 1800 U S P units of vitamin A and of not less than 400 U S P units of vitamin D

PARKE, DAVIS & COMPANY

Cod Liver Oil with Viosterol 90 cc. and 480 cc. bottles
Each 1 Gm. has a potency of not less than 2000 U S P units of vitamin A and of not less than 400 U S P units of vitamin D

E. R. SQUIBB & SONS

Cod Liver Oil with Viosterol 90 cc. and 480 cc. bottles
Each 1 Gm. has a potency of not less than 2000 U S P units of vitamin A and of not less than 440 U S P units of vitamin D

COD LIVER OIL CONCENTRATE (LIQUID) —

.	oil
.	ara-
.	ency
.	ram
.	nore

Concentrate (liquid) possesses
oil so far as these depend

Dosage.—Prophylactic: For liquids: 6 to 12 drops daily. For capsules: 1 or 2 capsules daily.

Cod liver oil concentrate is made under U. S. patent 1,690,091 (October 30, 1928; expired) or under U. S. patent 1,984,858 (December 18, 1934; expires 1951).

CLINADOL COMPANY, INC.

Cod Liver Oil Concentrate: 60 cc. bottles, packaged with a dropper designed to deliver approximately 1 minim per drop. An extract of the nonsaponifiable fraction of cod liver oil in maize oil, to which has been added saccharin (3 in 10,000) and oil of cassia, 2 per cent. Each 1 Gm. of the concentrate has a potency of not less than 60,000 U. S. P. units of vitamin A and of not less than 6,000 U. S. P. units of vitamin D.

U. S. trademark 279,325.

WHITE LABORATORIES, INC.

Cod Liver Oil Concentrate Liquid: Bulk. A cod liver oil concentrate dissolved in cod liver oil having a potency of not less than 55,000 U. S. P. units of vitamin A and of not less than 5,500 U. S. P. units of vitamin D per gram.

Cod Liver Oil Concentrate Liquid: 6 cc., 30 cc. and 60 cc. vials, packaged with a dropper designed to supply in each 2 drops (0.062 cc.) a potency of not less than 3,120 U. S. P. units of vitamin A and of not less than 312 U. S. P. units of vitamin D.

Capsules Cod Liver Oil Concentrate: 0.195 cc. Each capsule has a potency of not less than 5,000 U. S. P. units of vitamin A and of not less than 500 U. S. P. units of vitamin D.

COD LIVER OIL CONCENTRATE TABLETS.—Cod liver oil in the form of tablets having a potency of not less than 3,120 U. S. P. units of vitamin A and of not less than 312 U. S. P. units of vitamin D.

Actions and Uses.—Cod Liver Oil Concentrate Tablets possess properties similar to cod liver oil so far as these depend on the fat soluble vitamin content of the latter.

Dosage.—Two to six tablets daily.

WHITE LABORATORIES, INC.

Tablets Cod Liver Oil Concentrate: Each tablet has a potency of not less than 3,120 U. S. P. units of vitamin A and of not less than 312 U. S. P. units of vitamin D.

HALIBUT LIVER OIL WITH VIOSTEROL.—Halibut liver oil with Viosterol (ABBOTT) and (PARKE, DAVIS).—Halibut liver oil to which has been added sufficient viosterol (activated ergosterol) to assure a potency of not less than 10,000 U. S. P. units of vitamin D per gram.

Actions and Uses—The same as those for cod liver oil. See general article, *Vitamins A and D Preparations*

Dosage—For infants 10 drops (about 0.3 cc) daily, for preschool children 15 drops (about 0.42 cc) daily, for mothers 20 drops (about 0.4 cc) or more daily. The marketed preparation is accompanied by a special dropper designed to deliver a certain number of drops to the minimum.

ABBOTT LABORATORIES

Haliver Oil with Viosterol 5 cc., 20 cc. and 50 cc. bottles
U S trademark 294 692

Soluble Gelatin Capsules Haliver Oil with Viosterol 0.09 cc. Each capsule supplies 5,000 U S P units of vitamin A and 1,000 U S P units of vitamin D

INTERNATIONAL VITAMIN DIVISION, IVES CAMERON COMPANY, INC.

Halibut Liver Oil with Viosterol in Oil 10 cc. and 60 cc. bottles.

Soluble Gelatin Capsules Halibut Liver Oil with Viosterol in Oil: 0.195 cc. Each capsule supplies 5,000 U S P units of vitamin A and 1,700 U S P units of vitamin D

McKesson & Robbins, Inc.

Halibut Liver Oil with Viosterol in Oil 6 cc. and 60 cc. bottles

Soluble Gelatin Capsules Halibut Liver Oil with Viosterol in Oil: 0.195 cc. Each capsule supplies 8,500 U S P units of vitamin A and 1,700 U S P units of vitamin D

MEAD JOHNSON & COMPANY

Viosterol in Halibut Liver Oil 10 cc. and 50 cc. bottles

PARKE, DAVIS & COMPANY

Haliver Oil with Viosterol 5 cc., and 50 cc. bottles

Soluble Gelatin Capsules Haliver Oil with Viosterol: Each capsule supplies 5,000 U S P units of vitamin A and 1,000 U S P units of vitamin D
U S trademark 294 692

PERCOMORPH LIVER OIL—Oleum Percomorphum.

—A mixture containing the fixed oils obtained from the fresh livers of the percomorph fishes, principally *Xiphias gladius*.

morio, *Roccus lineatus*, *Cynoscion nobilis*, *Eriscion macdonaldi*, *Epinephelus analogus*, *Stereolepis ishinagi* and *Sphyræna argentea*, containing not more than 50 per cent of other fish liver oil. It is biologically assayed to have a potency of not less than 60,000 units of vitamin A (U. S. P.) per gram and of not less than 8,500 units of vitamin D (U. S. P.) per gram.

For tests and standards, see Section B.

Actions and Uses.—Same as those of cod liver oil. See general article, Vitamins A and D Preparations.

Dosage.—Prophylactic, for normal infants, 10 drops daily; curative, and in severe conditions, to 20 drops daily. The product is marketed with a dropper designed to deliver 44 drops to the cc.

AMERICAN PHARMACEUTICAL CO., INC.

Codanol Percomorph Liver Oil 50% with Viosterol:

FLINT, EATON & COMPANY

Oleum Percomorphum: 8 cc. bottle.

MEAD JOHNSON & COMPANY

Oleum Percomorphum with Other Fish-Liver Oils and Viosterol: A blend of liver oils of percomorph fishes, viosterol and other fish livers. A source of vitamin A and D in which not less than 50 per cent of the vitamin content is derived from the livers of percomorph fishes. Each gram contains not less than 60,000 U. S. P. units of vitamin A and 8,500 U. S. P. units of vitamin D.

Oleum Percomorphum with Other Fish-Liver Oils and Viosterol: 10 cc. and 50 cc. bottles.

Capsules Oleum Percomorphum with Other Fish-Liver Oils and Viosterol: Each capsule contains 83 mg. of oleum percomorphum with other fish liver oils and viosterol and supplies a potency of 5,000 U. S. P. units of vitamin A and 700 U. S. P. units of vitamin D.

SHARK LIVER OIL.—The oil extracted from the livers of the shark, mainly of the variety *Hypoprion brevirostris* (lemon), but any or all of the following varieties may be included: *Odontaspis littoralis* (sand), *Isurus punctatus* (mackerel), *Triakis semifasciatus* (leopard), *Sphyrna zygaena* (hammerhead), *Carcharias obscurus* (dusky), *Ginglymostoma cirratum* (nurse), *Carcharias milberti* (white) and *Carcharias limbatus* (black tip). It is biologically assayed and has a potency of not less than 16,500 units of vitamin A (U. S. P.) per gram.

and of not less than 40 units of vitamin D (U. S. P.) per gram; the latter is insignificant if taken according to directions.

For tests and standards, see Section B

Actions and Uses—See the general article, Vitamin A and D Preparations

Dosage.—One capsule, or about 0.52 cc., daily

Vitamin K Preparations

under Menadione and Menadione Tablets.

Actions and Uses—A synthetic naphthoquinone derivative having physiologic properties of vitamin K. See the general article, Vitamin K.

Dosage—From 1 to 2 mg daily or as prescribed by the

properties."

ABBOTT LABORATORIES

Tablets Kayquinone: 1 mg

Capsules Kayquinone: 1 mg.

U. S. trademark 382,006

GEORGE A. BREON & COMPANY, INC.

Tablets Menadione: 2 mg

R. E. DWIGHT & COMPANY

Capsules Menadione: 2 mg

ENDO PRODUCTS, INC

Solution Menadione in Oil: 2 mg per 2 cc., 2 cc. ampuls in corn oil

Tablets Menadione: 1 mg and 2 mg

LAKESIDE LABORATORIES, INC.

Capsules Menadione in Oil: 2 mg.

Solution Menadione in Oil: 2 mg. per cc. in sesame oil, 1 cc. ampuls. Preserved with chlorobutanol 0.5 per cent.

MCNEIL LABORATORIES

Capsules Menadione in Oil: 2 mg.

MERCK & Co., INC.

Menadione (Powder).

E. S. MILLER LABORATORIES, INC.

Solution Menadione in Oil: 1 mg. per cc., 1 cc. ampuls. Each cc. contains 1 mg. of menadione with benzocaine 2 per cent. Preserved with cresol 0.5 per cent.

Tablets Menadione: 1 mg.

SHARP & DOHME, INC.

Solution Menadione in Oil: 2 mg. per cc., in peanut oil, 1 cc. ampuls.

Tablets Menadione: 1 mg.

E. R. SQUIBB & SONS

Solution Thyloquinone in Oil: 2 mg. per cc., in corn oil, 1 cc. ampuls.

Capsules Thyloquinone in Oil: 1 mg. per cc., in corn oil. A brown gelatin capsule.

U. S. patents 2,455,397 and 2,455,398 (December 7, 1948, expires 1965); U. S. trademark 379,351.

U. S. VITAMIN CORPORATION

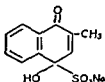
Capsules Menadione: 1 mg. and 2 mg.

Solution Menadione in Oil: 1 mg. per cc., in corn oil, 1 cc. ampuls.

THE VALE CHEMICAL Co., INC.

Tablets Menadione: 2 mg.

MENADIONE SODIUM BISULFITE - U. S. P. - Hykinone (ABBOTT).—Menadione Bisulfite.—“Contains not less than 49 per cent of menadione ($C_{11}H_8O_2$)”—U. S. P. Menadione Sodium Bisulfite has the following structural formula:



It may be prepared by the interaction of menadione and sodium bisulfite to form the addition product

For description and standards see the U S Pharmacopoeia under Menadione Sodium Bisulfite and Menadione Sodium Bisulfite Injection.

Actions and Uses—Menadione sodium bisulfite is used for essentially the same conditions as is menadione, which possesses the physiologic properties of vitamin K. Unlike menadione it is soluble in water, and stable aqueous solutions may be prepared. Since this material is water soluble oral administration is effective without the use of bile salts

Dosage—It may be administered subcutaneously intramuscularly or intravenously, the average daily dose being 0.5 to 2 mg. During administration of the drug the prothrombin level of the blood should be followed especially when there appears to be need of an additional dose during a twenty four hour period.

ABBOTT LABORATORIES

Solution Hykinone 72 mg. 10 cc ampuls Each 10 cc. contains Menadione U S P 72 mg. and Sodium Bisulfite 27.5 mg. in an aqueous solution made isotonic with sodium chloride

U S patent 2,367,302 (January 16, 1943) U S trademark 383,789

THE WM S MERRELL COMPANY

Solution Menadione Sodium Bisulfite 384 mg. per cc. 1 cc. ampuls Each cc. contains the equivalent of 2 mg. of menadione stabilized with 0.05 per cent sodium bisulfide

Tablets Menadione Sodium Bisulfite 384 mg.

U. S. Patent number 2,331,808

VITAMIN K₁ — 2-Methyl-3-Phtyl-1,4-Naphthoquinone.—

It may be isolated from natural sources or prepared by condensing 2-methyl-1,4-naphthoquinone with the suitable phtyl derivative.

For tests and standards see Section B

Actions and Uses—See the general article Vitamin K. It has been suggested that vitamin K₁ has a more prolonged effect than menadione

Dosage—From 4 mg. to 10 mg. by mouth with or without bile salts. Intravenous dose for adults may be as much as 10 mg. dispersed in dextrose solution. For newborn infants a dose of 0.25 mg. may be administered intravenously

MERCK & CO. INC.

Vitamin K₁ 1 Gm. 5 Gm. and 25 Gm. ampuls

Mixed Vitamin Preparations

HEXAVITAMIN U S P—Hexavitamin Capsules and Tablets contain in each capsule or tablet not less than 5,000

SECTION B

Tests and Standards

Section B of New and Nonofficial Remedies contains chemical and physical descriptions, and methods for the identification and standardization of Council accepted drugs for which official standards are not available. These methods have been developed jointly by the A. M. A. Chemical Laboratory and the firms submitting preparations to the Council. The Tests and Standard in this section are arranged alphabetically according to the non-protected (generic) names of the drugs.

The test solutions required in the qualitative and quantitative tests have been designated by their official names and unless otherwise stated, the strengths are those specified in the U. S. P. XIII. Percentage, where it is used for specifying strengths of solutions means "weight over volume", exceptions are stated when they occur.

All the common tests, i. e. for absence of heavy metals, sulfates and chlorides, are performed as described in detail in U. S. P. XIII. Less common tests are given either in the individual monographs or in the references cited.

The A. M. A. Chemical Laboratory currently is engaged in a critical examination of the analytical methods appearing in this Section of New and Nonofficial Remedies. Criticism from other analysts will be appreciated.

Absorbable Gelatin Sponge—A sterile absorbable water-insoluble gelatin base sponge.

Absorbable gelatin sponge is obtained by foaming a specially prepared skin gelatin solution which is then dried in air and subsequently sterilized by dry heat at 149° C.

Absorbable gelatin sponge is a light, nearly white, nonelastic, rough, porous matrix that may be cut into any shape or size. It shows no tendency to disintegrate even with relatively rough handling. A piece of absorbable gelatin sponge may be rapidly wetted by working it vigorously between moistened fingers and it will then readily imbibe water. A 10 mm. tube of absorbable gelatin sponge weighing approximately 9 mg. will take up approximately fifty times its weight of water or forty five times its weight of well agitated oxalated whole blood. Absorbable gelatin sponge will withstand dry heat at 150° C.

Add 5 cc. of 1 % sodium hydroxide to a small piece of absorbable gelatin sponge and gently heat the mixture. Then add lead acetate T. S. a white precipitate forms (distinction from fibrin foam). Add 2 or 3 cc. of Millon's reagent to a small piece of absorbable gelatin sponge; there is no change in color (distinction from fibrin foam). The residue on ignition should not exceed 20 mg. per gram of absorbable gelatin sponge.

Place a 50 mg. piece of absorbable gelatin sponge in a beaker of distilled water. Squeeze the absorbable gelatin sponge out gently between the fingers until the sponge is thoroughly wet; care being taken not to break the tissue.

Lift from the water and remove the excess water with absorbent paper. Place the wetted sample in a 150 cc. stoppered flask which contains 100 cc of a 1 per cent solution of pepsin N.F. in tenth-normal hydrochloric acid previously warmed to 37° C. Maintain at a temperature of 37° C., and agitate gently and continuously until digestion is complete. The average digestion time is less than 30 minutes.

ACETPYROGALL.— $C_{12}H_{12}O_6$ —M. W. 252.22.—Triacetyl pyrogallol.

Acetpyrogall is a white, crystalline powder, melting at 165° C. It is insoluble in water, but soluble with decomposition in warm aqueous alkalis. It is incompatible with alkalis, strong acids and oxidizing agents.

AFENIL (BILHUBER-KNOLL).— $C_4H_{16}CaCl_2N_8O_4$.—F. W. 351.2.—A molecular compound of calcium chloride and urea, $CaCl_2 \cdot 4(NH_2)_2CO$.

This compound occurs as colorless crystals; non hygroscopic; very soluble in water.

The calcium content is determined by precipitating with ammonium oxalate in the usual way and weighing as calcium oxide. The urea content is determined by an estimation of nitrogen by the Kjeldahl method.

ALLYL BARBITURIC ACID.— $C_{11}H_{16}N_2O_3$ —M. W. 224.25.—5-Isobutyl-5-allyl barbituric acid.

occurs. To the other portion add 0.1 cc potassium permanganate T.S.: a yellow color appears immediately, turning to brown.

ALUMINUM HYDROXIDE GEL.—N. N. R.—An aqueous suspension containing not less than 3 per cent nor more than 4.2 per cent of aluminum oxide (Al_2O_3 —F. W. 101.94), chiefly in the form of aluminum hydroxide ($\text{Al}(\text{OH})_3$ —F. W. 77.99). Flavoring, sweetening and preservatives may be added.

See also standards of the U. S. Pharmacopeia under Aluminum Hydroxide Gel.

Aluminum hydroxide gel occurs as a white or light gray suspension which may settle out to some extent or form a semisolid on standing but which liquefies on shaking. The specific gravity at 25 C is from 1.030 to 1.042.

Transfer about 5 Gm. of aluminum hydroxide gel to a glass container and add 10 cc. of diluted hydrochloric acid; the solution is clear and colorless within ten minutes; to this solution add 8 cc. of diluted ammonia solution; a flocculent precipitate appears which is insoluble in excess diluted ammonia solution but soluble in sodium hydroxide solution. To about 5 Gm. of aluminum hydroxide gel in an Erlenmeyer flask add 10 cc. of sodium hydroxide T.S. and boil; the fumes do not turn moistened red litmus paper to blue (ammonia).

Dissolve 10 Gm. of aluminum hydroxide gel in 10 cc. of diluted hydrochloric acid and boil. Cool, dilute to 250 cc. and filter if necessary. To 10 cc. add 1 cc. of barium chloride T.S. and allow to stand for ten minutes; the turbidity is not greater than that produced by 0.2 cc. of fiftieth normal sulfuric acid in 10 cc. of water.

The pH at 25 C. of aluminum hydroxide gel is between 6.4 and 7.2. Dissolve 25 Gm. of the gel in 5 cc. of diluted sulfuric acid and boil; the solution meets the U. S. P. test for arsenic. Dissolve 10 Gm. of aluminum hydroxide gel in 10 cc. of diluted sulfuric acid; the resultant solution conforms to the U. S. P. test for heavy metals.

Transfer 25 Gm. of aluminum hydroxide gel, accurately weighed to an Erlenmeyer flask, add 25 cc. of distilled water and 0.2 cc. of potassium chromate T.S. Titrate with tenth normal silver nitrate to a faint pink color; the chlorine content is not greater than 0.35 per cent.

Transfer about 3 Gm. of aluminum hydroxide gel, accurately weighed to an Erlenmeyer flask, dilute to 50 cc. and maintain at 37.5 C. Titrate with tenth normal hydrochloric acid during forty minutes, adding the acid in 0.5 cc. portions toward the end of the titration, using bromophenol blue T.S. as indicator; the volume of tenth-normal acid used is not more than 2.500 cc., nor less than 1.250 cc. per hundred Gm.

Transfer about 3 Gm. of aluminum hydroxide gel, accurately weighed, to a 250 cc. beaker and dilute to 100 cc. Add 10 cc. of diluted hydrochloric acid; heat to boiling and make the mixture alkaline to methyl red with diluted ammonia solution. Dilute to 200 cc., heat to boiling and wash four times by decantation. Filter and wash the precipitate free of chlorides with an aqueous solution containing 1 part of diluted ammonia solution in 25 parts of solution. Dry the precipitate and ignite at 900 C. to constant weight; the aluminum oxide content is not less than 1 nor more than 4.2 per cent.

AMOBARBITAL.— $\text{C}_{11}\text{H}_{19}\text{N}_2\text{O}_4$ —M. W. 226.27—5 Isobutyl 5-ethylbarbituric acid.

Amobarbital occurs as a white crystalline, odorless powder with a slightly bitter taste. It is completely soluble in alcohol and ether, very slightly soluble in cold water and insoluble in the paraffin hydrocarbons. A saturated aqueous solution is acid to litmus paper. It melts at 156-159.5° C. (U. S. P. cert.).

Place 0.3 Gm. of amobarbital in a 25 cc. glass stoppered cylinder, add a mixture of 1 cc. sodium hydroxide T.S. and 5 cc. of water; shake the contents for one minute, filter through paper and divide into two portions. To one portion add 1 cc. of mercuric bichloride T.S.; a white precipitate results, soluble in 10 cc. of diluted ammonia solution. To the other portion add 5 cc. of silver nitrate T.S.; a white precipitate results, soluble in 5 cc. of diluted ammonia solution. Dissolve 0.3 Gm. of amobarbital with 5 cc. of a 25 per cent sodium hydroxide solution; it is decomposed with the evolution of ammonia.

ethylbarbituric acid.

AMOBARBITAL SODIUM.— $C_{11}H_{17}N_2NaO_3$.—M. W. 248.26.—The monosodium salt of 5-isoamyl-5-ethylbarbituric acid.

Amobarbital sodium occurs as a white, friable, hygroscopic, odorless, granular powder with a slightly bitter taste; very soluble in water; freely soluble in alcohol, about 1 part in 1 part; practically insoluble in ether.

Dissolve about 0.5 Gm. of amobarbital sodium in 100 cc. of water, add an excess of diluted hydrochloric acid, collect the resultant isoamyl-ethylbarbituric acid on a filter, wash and dry; it melts at 156-158.5° C. (U. S. P. corr.) Incinerate about 1 Gm. of amobarbital sodium: the residue responds to tests for sodium carbonate. Boil about 0.5 Gm. of amobarbital sodium with 5 cc. of a 25 per cent sodium hydroxide solution: it is decomposed with the evolution of ammonia. Dissolve about 0.3 Gm. of amobarbital sodium in 50 cc. of water and divide into two portions. To one portion add a white precipitate results. To the other portion add results, soluble in 5 cc. of

1 in 50 cc. of water, add paper: separate portions. Hence on the addition of turbidity on the addition of 0.2 Gm. of amobarbital acid hydrochloric acid and

tion with hydrogen sulfide. amobarbital sodium to 1 (readily carbonisable sub: sodium, accurately weighed anhydrous ether, stopper

weight at 90° C. 0.5 Gm. of amobarbital sodium, accurately weighed, to a suitable Squibb separatory funnel, add 50 cc. of water, followed by the addition of 10 cc. of diluted hydrochloric acid, extract with eight successive portions of ether, using 25 cc. each, evaporate the combined ethereal extracts to dryness in a stream of warm air and dry to constant weight at 90° C.: The amount of isoamylethylbarbituric acid corresponds to not less than 90 per cent nor more than 91.6 per cent (theory 91.15 per cent), calculated to the dried substance. Transfer the acidulated aqueous portion from the foregoing extraction to a tared platinum dish and evaporate to dryness on a steam bath; to the residue obtained add 5 cc. of sulfuric acid and heat cautiously until the excess of sulfuric acid has been volatilized; repeat twice, using 1 cc. of sulfuric acid each time, add about 0.5 Gm. of ammonium carbonate, ignite to constant weight and weigh as

sodium sulfate. The percentage of sodium corresponds to not less than 8.9 per cent nor more than 9.5 per cent when calculated to the dried substance.

AMPHETAMINE.— $C_9H_{13}N$.—M. W. 135.20—*d,l*-1-Phenyl-2-aminopropane—Racemic desoxynor-ephedrine.

Amphetamine occurs as a colorless, mobile liquid, boiling at 200–203° C. with slight decomposition. The specific gravity at 25° C. is 0.931. The vapor pressure at ordinary temperature is relatively high, and the substance possesses a strong basic odor and a burning taste.

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weighing bottle and place on the steam bath for one hour. The residue is not more than 0.5 per cent (*nonvolatile compounds*). Dissolve 1 cc. of amphetamine in 10 cc. of liquid petrolatum U. S. P. (anhydrous); no turbidity is produced (*water*).

Suspend about 1 Gm. of amphetamine, accurately weighed, in 10 cc. of water and titrate with half-normal sulfuric acid, using methyl

than 0.275 Gm. per tube.

Transfer the solution from the titration to a separatory funnel, extract with 30 cc. of ether, transfer the aqueous layer to an Erlenmeyer flask, add 2 cc. of 40 per cent sodium hydroxide solution and a total of 1.5 cc. of benzoyl chloride, 0.5 cc. at a time, shaking the flask and contents thoroughly after each addition and allowing the reaction mixture to set for one hour before the next portion of benzoyl chloride is added; heat on a steam bath until the odor of benzoyl chloride has disappeared, remove the precipitate by filtration, wash with cold water and dry at 90° C.; the melting point is 130–135° C.

AMPHETAMINE SULFATE.— $C_{18}H_{23}N_2O_4S$ —M. W. 368.48—*d,l*-1-Phenyl-2-aminopropane sulfate—Racemic desoxy-nor-ephedrine sulfate.

Amphetamine sulfate occurs as a white, odorless powder; freely soluble in water, slightly soluble in alcohol, insoluble in ether. A solution of 1 Gm. in 10 cc. of water has a pH between 5.0 and 6.0. Amphetamine sulfate melts above 300° C., with decomposition.

Place 1 Gm. of amphetamine sulfate in an Erlenmeyer flask, add 50 cc. of water and 5 cc. of 40 per cent sodium hydroxide solution; then add benzoyl chloride, 0.5 cc. at a time, shake the flask after each addition; add the benzoyl chloride until no more precipitate forms after an addition. Recrystallize the derivative twice from 50 per cent alcohol and dry the crystals, which melt at 134–135° C. The nitrogen content of the benzoyl derivative by the micro Dumas method is not less than 5.70 per cent nor more than 5.95 per cent.

Dry about 0.5 Gm. of amphetamine sulfate, accurately weighed, to constant weight at 100° C.; the loss does not exceed 1 per cent. Incin-

erate about 0.5 Gm. of amphetamine sulfate, accurately weighed; the residue is not more than 0.1 per cent.

Transfer 0.5 Gm. of amphetamine sulfate, accurately weighed, to a beaker and dissolve in 200 cc. of water and 2 cc. of normal hydrochloric acid. Boil and add 10 cc. of boiling 10 per cent barium chloride T.S. Allow to stand overnight, filter, wash until free from chloride, ignite at low red heat to constant weight, cool, and weigh; the sulfate content is not less than 25.5 per cent nor more than 26.4 per cent.

Dissolve 0.25 Gm. of amphetamine sulfate, accurately weighed, in 25 cc. of water in a separatory funnel. Add 5 cc. of 10 per cent sodium hydroxide solution and extract with six 15 cc. portions of ether. Filter the ether extracts into a glass stoppered flask and shake with 20 cc. of tenth-normal sulfuric acid. Evaporate the ether on a steam bath; add one drop of methyl red T.S. and titrate the excess acid with tenth-normal sodium hydroxide solution; the amphetamine content is not less than 72 per cent nor more than 73.5 per cent.

AMPROTROPINE PHOSPHATE.— $C_{18}H_{22}NO_7P$.—M. W. 405.42.—The phosphate of *d,l*-tropic acid ester of 3-diethyl-amino-2,2-dimethyl-1-propanol.

Amprotropine phosphate occurs as a white, crystalline powder, with a faint roseate odor and a bitter taste. It is freely soluble in water, slightly soluble in absolute alcohol and insoluble in chloroform and ether. The aqueous solution is acid to litmus. Amprotropine phosphate melts at 142° to 145° C. From aqueous solutions, alkali hydroxides precipitate the free base as a water-white oil, which does not solidify at ordinary temperatures.

Place about 0.01 Gm. of amprotropine phosphate in a porcelain dish, add a few drops of nitric acid, and evaporate to dryness on a water bath; a yellow residue results; cool, add a few drops of alcoholic potassium hydroxide solution; the mixture is a violet color.

Dry about 0.5 Gm. of amprotropine phosphate, accurately weighed, to constant weight at 100° C.; the loss in weight does not exceed 1 per cent. Incinerate about 0.5 Gm. of amprotropine phosphate, accurately weighed, in a platinum crucible; the residue does not exceed 0.1 per cent. Transfer about 0.5 Gm. of amprotropine phosphate to a 500 cc. Kjeldahl flask and determine the nitrogen content according to the official method described in *Methods of Analysis of the Association of Official Agricultural Chemists*, ed. 6, p. 27, paragraph 25; the percentage of nitrogen corresponds to not less than 3.3 per cent nor more than 3.6 per cent when calculated to the dried substance.

AMYLSINE HYDROCHLORIDE (NOVOCOL).— $C_{14}H_{22}O_2N_2HCl$.—M. W. 286.79.—2-*p*-Aminobenzoxyl-1-*n*-amylaminoethane hydrochloride.

2-*p*-Aminobenzoxyl-1-*n*-amylaminoethane hydrochloride occurs as a fine, white, odorless powder which, when applied to the tongue, produces a bitter taste followed by a sense of numbness. It is soluble in water, sparingly soluble in ethanol and insoluble in ether, benzene and chloroform. An aqueous solution is acid to litmus. The free base separates as a solid from the hydrochloride solutions on the addition of sodium hydroxide or carbonate T.S. but not with 5 per cent sodium bicarbonate solution. The hydrochloride occurs in dimorphic forms. The form which crystallizes from amyl alcohol melts at 176° C., while the one crystallized from water melts at 153.5° C.; the free base melts at 65° C.

Dissolve 0.1 Gm. of 2-*p*-aminobenzoxyl-1-*n*-amylaminoethane hydrochloride in 50 cc. of water; to one 5 cc. portion add 1 cc. of silver nitrate solution, 10 cc. of diluted ammoniacal silver nitrate, 10 cc. of diluted ammoniacal silver nitrate, and 1 cc. of a

saturated solution of sodium nitrite and heat to 50° C. a yellow oil separates (*distinction from butyn, cocaine, procaine and tetracaine*) Dissolve 0.1 Gm of the hydrochloride in 1 cc of sulfuric acid the solution is colorless (*readily carbonizable substances*) Saturate a solution of 0.1 Gm in 10 cc of water with hydrogen sulfide no coloration or precipitation occurs (*salts of heavy metals*)

Transfer about 0.5 Gm of 2-*p*-aminobenzoyl-1-n-amylnaminoethane hydrochloride accurately weighed to a tared platinum dish and dry at 100° C. for six hours the loss in weight does not exceed 3 per cent Incinerate about 0.5 Gm of the hydrochloride, accurately weighed the ash does not exceed 0.1 per cent Transfer a sample of the hydrochloride previously dried and accurately weighed to a Kjeldahl flask and digest with sulfuric acid in the presence of 0.1 Gm of selenium dilute make alkaline with 40 per cent sodium hydroxide solution distil into standard acid and titrate the excess acid is not greater than 98 nor 1 Gm of the hydrochloride to a 250 cc beaker and dissolve and add 1 cc of nitric acid on the steam bath for three precipitate the chlorine content 12.0 per cent.

ANTHRALIN— $C_{14}H_{10}O_3$ —M W 226.22—1,8,9 Anthra triol

Anthralin occurs as an odorless and tasteless yellow, crystalline powder which is readily soluble in chloroform soluble in acetone, benzene and pyridine, slightly soluble in alcohol ether and glacial acetic acid, and insoluble in water It is soluble in sodium hydroxide T.S., yielding a yellow to orange colored solution possessing greenish fluorescence Alkaline solutions of anthralin rapidly oxidize in air, lose fluorescence and become a deep orange red The melting point of anthralin is from 175° to 181° C.

Dissolve about 0.1 Gm of anthralin in 10 cc of alcohol and 0.1 cc of diluted ferric chloride T.S. a greenish brown color results Add a few crystals of anthralin to 2 cc of sulfuric acid an orange-yellow color results (*1,8-dihydroxyanthraquinone gives a scarlet color*)

Dissolve 0.1 Gm of anthralin in 10 cc of warm acetone the solution is clear pour the solution into 200 cc of water a yellow precipitate results Add 5 cc of sodium hydroxide T.S. and mix the precipitate dissolves and the yellow colored solution rapidly changes to orange and finally to red

Add about 0.5 Gm of anthralin to a mixture of 3 cc of anhydrous pyridine and 3 cc of acetic anhydride and boil about fifteen minutes Pour the mixture on crushed ice collect the precipitate and recrystallize twice from glacial acetic acid the melting point of the yellow needle shaped crystals of triacetyl anthralin obtained is from 203° to 210° C., with sublimation

Add 0.5 Gm of anthralin to 10 cc of water mix and filter the filtrate is neutral separate portions of the filtrate yield no turbidity on the addition of silver nitrate T.S. barium nitrate T.S. or ammonium sulfide T.S. and no color on the addition of ferric chloride T.S.

Ignite 0.5 Gm of anthralin the ash is negligible

Transfer 0.1 Gm of anthralin accurately weighed to a beaker add 75 cc of acetone and warm to dissolve the solid While the solution is hot add 10 cc of silver ammonium nitrate solution (dissolve 3 Gm of silver nitrate in 120 cc of water and add 10 cc of 10 per cent ammonium hydroxide solution) mix and allow to stand at room temperature for two hours Filter through a suitable Gooch crucible (or sintered glass filter) Wash the beaker and precipitate with ether, acetone then about 300 cc of ammoniacal ammonium nitrate solution (dissolve 15 Gm of ammonium nitrate in 300 cc of water and add 10 cc of strong ammonia solution) and finally wash with acetone Place the filter in the beaker used for the precipitation of silver, add 10 cc of water and 10 cc of nitric acid and heat to near boiling to facilitate solution of the silver Add enough water to cover the filter and boil gently for twenty minutes Add 0.5 Gm of chloride free

decolorizing charcoal, mix, let stand for ten minutes and filter while hot through paper. Rinse the beaker and crucible with hot water and finally wash the paper and residue with hot water; combine the filtrate and washings. Cool and titrate with tenth-normal ammonium thiocyanate, using 5 cc. of ferric ammonium sulfate T.S., acidified with nitric acid, as the indicator. Each cubic centimeter of tenth normal ammonium thiocyanate is equivalent to 0.01079 Gm. of silver. The amount of silver precipitated, calculated from the titration, is not less than 1.35 times and not more than 1.45 times the amount of anthralin taken.

ANTIMONY THIOGLYCOLLAMIDE.— $C_6H_{12}N_3O_3S_3Sb$.—M. W. 392.13.—The triamide of antimony thioglycollic acid, $Sb(S.CH_2CO.NH_2)_3$.

Antimony thioglycollamide is a white, crystalline, odorless powder. It is soluble in about 200 parts of water, somewhat soluble in alcohol and insoluble in ether.

Dissolve 0.2 Gm. of antimony thioglycollamide in 5 cc. of hydrochloric acid, add 10 cc. of freshly prepared stannous chloride solution and allow to stand 30 minutes; no brownish tint or precipitate is visible if viewed from above over a white surface (arsenic). A blank test should be carried out, using the same quantities of reagents.

Weigh accurately from 0.2 to 0.3 Gm. of antimony thioglycollamide, dissolve it in about 100 cc. of warm water, add 1 cc. of diluted hydrochloric acid, pass in hydrogen sulfide until precipitation is complete and allow to stand 30 minutes. Collect the antimony sulfide in a weighed Gooch crucible; wash it successively with water containing hydrogen sulfide, alcohol, ether, carbon disulfide, alcohol and ether; dry the residue at $100^\circ C$; and weigh. The antimony sulfide obtained corresponds to not less than 30 per cent of antimony.

Place about 0.3 Gm. of aprobarbital in a glass stoppered cylinder, add a mixture of 1 cc. of normal sodium hydroxide solution and 5 cc. of water, shake contents for 1 minute, filter through paper and divide into two portions. To one portion add 1 cc. of mercury bichloride T.S.; a white precipitate results, soluble in an excess of diluted ammonia solution. To the other portion add 5 cc. of silver nitrate T.S.; a white precipitate results, soluble in an excess of diluted ammonia solution. Boil about 0.5 Gm. of aprobarbital with 5 cc. of a 25 per cent sodium hydroxide solution; it is decomposed with the evolution of ammonia. Dissolve about 0.1 Gm. of aprobarbital in 1 cc. of sulfuric acid; not more than a slight yellow color results. Place about 1 Gm. of aprobarbital in a 25 cc. glass stoppered cylinder, add 10 cc. of water, shake the mixture for one minute, filter through one portion add 1 cc. of acetic acid; immediate discoloration occurs. To the other portion add 1 cc. of potassium permanganate T.S.; turning to brown.

Boil about 0.5 Gm. of aprobarbital with 50 cc. of water for two minutes; no odor develops; cool and filter; separate portions of 10 cc. each of the filtrate yield no opalescence with 1 cc. of diluted nitric acid and 1 cc. of silver nitrate T.S. (chloride); no turbidity with 1 cc. of

diluted nitric acid and 1 cc of barium nitrate T.S. (*sulfate*); no coloration or precipitation on saturation with hydrogen sulfide (*salts of heavy metals*). Ash about 1 Gm of aprobarbital, accurately weighed there is not more than 0.1 per cent residue. Dissolve about 0.5 Gm of aprobarbital, accurately weighed, in 25 cc of previously neutralized alcohol. Dilute with an equal volume of water previously boiled to remove carbon dioxide and titrate with tenth normal sodium hydroxide solution, using thymolphthalein T.S. as an indicator. The amount of tenth normal sodium hydroxide solution consumed corresponds to not less than 98.5 per cent nor more than 101.5 per cent allyl isopropylbarbituric acid.

APROBARBITAL SODIUM.— $C_{10}H_{13}N_2NaO_3$ —M. W. 232.22.—The monosodium salt of 5-allyl-5-isopropylbarbituric acid.

Aprobarbital sodium is a white microcrystalline, hygroscopic, odorless powder, with a slightly bitter taste, very soluble in water, very slightly soluble in alcohol, practically insoluble in ether. An aqueous solution of aprobarbital sodium is alkaline to litmus.

In an excess of diluted ammonia solution

of aprobarbital sodium to 1 cc of sulfuric acid the solution is colorless (*readily carbonizable substances*). Transfer about 1 Gm of aprobarbital sodium, accurately weighed, to a glass stoppered cylinder, add 30 cc of anhydrous ether, stopper and shake for ten minutes, decant the supernatant liquid through filter paper and repeat twice, using 25 cc, and 15 cc portions, respectively, of ether, utilizing the same filter. Evaporate the combined filtrates to dryness in a tared beaker and dry to constant weight at 90° C. the residue does not exceed 0.2 per cent (*uncombined allylisopropyl barbituric acid*).

extraction to a tared platinum dish and evaporate to dryness on a steam bath, to the residue obtained add 5 cc of sulfuric acid, heat cautiously

tive of arspenamine methylene sulfonic acid (the exact structural formula of which has not been established) with inorganic salts. It contains approximately 13 per cent of arsenic and 24 per cent of bismuth.

Bismuth arspenamine sulfonate is a brownish-yellow amorphous powder readily soluble in water, yielding a yellow solution which is slightly alkaline to litmus.

Add 2 cc. of diluted hydrochloric acid to 5 cc. of a 1 per cent solution of bismuth arspenamine sulfonate: a white opalescence appears and dissolves almost immediately; a heavy white gelatinous precipitate develops in two minutes. Add 1 cc. of diluted nitric acid to 5 cc. of a 1 per cent solution of bismuth arspenamine sulfonate: the solution gradually turns brown. Add 5 cc. of a 1 per cent solution of bismuth potassium sulfonate: the solution is at first turbid, then becomes a deep reddish brown with formation of a precipitate. Add 1 cc. of mercuric potassium iodide T.S. to 5 cc. of a 1 per cent solution of bismuth arspenamine sulfonate: the solution yields a greenish-yellow opalescence, which in turn assumes a dirty green color on standing. Add drop by drop 2 cc. of a 40 per cent sodium hydroxide solution to 5 cc. of a 1 per cent solution of bismuth arspenamine sulfonate: the solution gradually darkens without any formation of precipitate. Add 0.5 cc. of a 2 per cent silver nitrate solution to 5 cc. of a 1 per cent solution of bismuth arspenamine sulfonate: a dark red solution is produced (distinction from arspenamine). Add 1 cc. of bromine T.S. to 5 cc. of a 1 per cent solution of bismuth arspenamine sulfonate. The solution yields a greenish brown precipitate (distinction from sulfarsamine). Add 0.5 Gm. of zinc to 0.1 Gm. of bismuth arspenamine sulfonate: the mouth of the tube hold a stratum cadmium chloride solution: the solution is at first turbid, then becomes a deep reddish brown with formation of a precipitate.

Transfer about 0.4 Gm. of weighed, to a Kjeldahl flask, fully; add 2 cc. of nitric acid brown fumes cease to be given off; add 2 cc. of hydrochloric acid, transfer to a 250 cc. beaker, add 10 cc. of magnesia mixture followed by 20 cc. strong ammonia solution, allow to stand 12 hours, filter through a hard surfaced filter paper and wash the precipitate with 50 cc. of 2.5 per cent diluted ammonia solution, puncture the filter, transfer the precipitate into a 250 cc. beaker with washings, then add just sufficient hydrochloric acid to dissolve the precipitate, filter, wash the filter well with water, neutralize the filtrate with strong ammonia solution; add 1 cc. of magnesia mixture and 20 cc. of strong ammonia solution; allow to stand 12 hours, filter, using a prepared Gooch crucible; wash with 2.5 per cent diluted ammonia solution; dry at 100° C.; ignite at 700° C. for three hours; cool in a desiccator and weigh as magnesium pyroarsenate and calculate to arsenic: the arsenic content is not less than 12.50 per cent nor more than 13.50 per cent. Transfer about 0.25 Gm. of bismuth arspenamine sulfonate, accurately weighed, to an Erlenmeyer flask. Add 5 cc. of diluted sulfuric acid followed by 1 Gm. of powdered potassium permanganate, and 10 cc. of sulfuric acid in small portions; add just sufficient hydrogen peroxide solution to dissolve the brown precipitate, add 50 cc. of water; boil for 20 minutes; cool to 70° C.; saturate with hydrogen sulfide, then stopper the flask and allow it to stand for 12 hours; filter, using a prepared Gooch crucible; wash the precipitate with water, warm ammonium polysulfide, methyl alcohol, carbon bisulfide and acetone in the order named; dry at 100° C.; cool in a desiccator and weigh as bismuth sulfide.

acid, neutralize with strong ammonia water and add 10 cc. of magnesia mixture followed by 20 cc. strong ammonia solution, allow to stand 12 hours, filter through a hard surfaced filter paper and wash the precipitate with 50 cc. of 2.5 per cent diluted ammonia solution, puncture the filter, transfer the precipitate into a 250 cc. beaker with washings, then add just sufficient hydrochloric acid to dissolve the precipitate, filter, wash the filter well with water, neutralize the filtrate with strong ammonia solution; add 1 cc. of magnesia mixture and 20 cc. of strong ammonia solution; allow to stand 12 hours, filter, using a prepared Gooch crucible; wash with 2.5 per cent diluted ammonia solution; dry at 100° C.; ignite at 700° C. for three hours; cool in a desiccator and weigh as magnesium pyroarsenate and calculate to arsenic: the arsenic content is not less than 12.50 per cent nor more than 13.50 per cent. Transfer about 0.25 Gm. of bismuth arspenamine sulfonate, accurately weighed, to an Erlenmeyer flask. Add 5 cc. of diluted sulfuric acid followed by 1 Gm. of powdered potassium permanganate, and 10 cc. of sulfuric acid in small portions; add just sufficient hydrogen peroxide solution to dissolve the brown precipitate, add 50 cc. of water; boil for 20 minutes; cool to 70° C.; saturate with hydrogen sulfide, then stopper the flask and allow it to stand for 12 hours; filter, using a prepared Gooch crucible; wash the precipitate with water, warm ammonium polysulfide, methyl alcohol, carbon bisulfide and acetone in the order named; dry at 100° C.; cool in a desiccator and weigh as bismuth sulfide.

(Bi_2S_3); calculate to bismuth: the percentage of bismuth found corresponds with the percentage of arsenic found multiplied by 1.86 (factor As to Bi in $\text{C}_{21}\text{H}_{21}\text{O}_{12}\text{As}_2\text{Na}_3\text{S}_2\text{N}_3\text{Bi}_2$) plus or minus 0.5 per cent.

BISMUTH CAMPHOCARBOXYLATE.— $\text{C}_{33}\text{H}_{46}\text{Bi}_2\text{O}_{11}$ —F. W. 10367—A basic bismuth salt of camphocarboxylic acid having the probable formula $(\text{C}_{10}\text{H}_{15}\text{OCOO})_2\text{BiOBi}(\text{C}_{10}\text{H}_{15}\text{OCOO})\text{OH}$.

Bismuth camphocarboxylate occurs as a white powder having the odor of camphor. It is insoluble in water but soluble in ether, benzene and vegetable oils.

Heat 1 Gm of bismuth camphocarboxylate in 30 cc of water containing 3 cc of hydrochloric acid, add diluted ammonia solution until resulting solution is alkaline to litmus, filter and wash the precipitate with 10 cc of water; to the filtrate add hydrochloric acid until just acid to litmus, evaporate on the steam bath until the volume is reduced one half, cool, filter and dry the crystals: the crystals melt at 127°C . Dissolve 0.1 Gm of the crystals in 5 cc of alcohol, add a drop of diluted ferric chloride solution (ferric chloride T.S. diluted 1 to 5) a green color results. Dissolve the precipitate (obtained from the treatment with diluted ammonia solution) in diluted hydrochloric acid and pass in hydrogen sulfide a black precipitate forms. Suspend 0.2 Gm of bismuth camphocarboxylate in 10 cc of boiling water and add 2 Gm of sodium hydro-sulfite a black precipitate forms.

nitric acid to dissolve the residue when warmed, pour the acid solution

minutes, decolorize with hydrogen peroxide, add 45 cc of water, boil for 15 minutes, pass in hydrogen sulfide until the bismuth is completely precipitated filter through a prepared Gooch crucible, wash with water, alcohol, chloroform and ether in this order, dry in an oven for 30 minutes at 100°C , cool in a desiccator and weigh, repeat the washing with chloroform and ether and the drying at 100°C until constant weight is attained. The weight of bismuth sulfide corresponds to not less than 37 nor more than 40 per cent bismuth.

BISMUTH ETHYLCAMPHORATE.— $\text{C}_{36}\text{H}_{57}\text{BiO}_{12}$ —M. W. 890.8—The bismuth III salt of *d*-camphoric acid mono-ethyl ester

Bismuth ethylcamphorate occurs as a white amorphous solid, possessing a faint aromatic odor. It is insoluble in water but soluble in

chloroform, ether, ethylene dichloride and vegetable oils. Its solubility in vegetable oils is increased by the addition of camphor. Bismuth ethylcamphorate softens at about 55° C. and melts in the range between 61 and 67 C.

Dissolve about 0.25 Gm. of bismuth ethylcamphorate in 25 cc. of ether in a separator; add diluted sulfuric acid sufficient to redissolve the white precipitate which forms at first; shake the mixture and then separate and wash the ether layer once with water; the aqueous acid layer responds to tests for bismuth. Extract the ether layer twice with 25 cc. portions of sodium hydroxide T.S., evaporate the combined alkaline extracts in a beaker to a volume of about 15 cc., cover the beaker with a watch glass and continue to heat for about two hours; filter, cool and acidify the solution with diluted sulfuric acid and allow the precipitate to crystallize. Separate and recrystallize the product from a small amount of hot water. The melting point of the dried *d*-camphoric acid obtained is from 186 to 188 C.

Place 0.25 Gm. of bismuth ethylcamphorate, accurately weighed, in a tared, low form weighing bottle; heat at 75-80° C. under pressure of 10 to 15 mm. of mercury to constant weight; the loss in weight is not more than 2.5 per cent.

Transfer about 0.5 Gm. of bismuth ethylcamphorate, accurately weighed, to a 500 cc. Kjeldahl flask, add 15 cc. of sulfuric acid and 15 cc. of nitric acid and boil gently until the mixture is colorless, adding more nitric acid if necessary. Continue to boil until the excess nitric acid is removed; cool and transfer the acid solution to a beaker, rinsing the flask with several 15 cc portions of water. Dilute to about 100 cc. add two drops of methyl red T.S. and add diluted ammonia solution dropwise until the solution turns yellow. Add 2 cc. of nitric acid and dilute to about 150 cc. Heat to boiling, add five drops of 10 per cent ammonium phosphate solution and stir vigorously. Then add 40 cc. of the phosphate solution and digest the precipitate on a steam bath for 30 minutes, filter through a tared Gooch crucible and wash the precipitate with 3 per cent ammonium nitrate solution acidified with diluted nitric acid. Dry at 100° C. for 30 minutes and finally ignite to constant weight. The weight of the bismuth phosphate found corresponds to a bismuth content of not less than 21.5 per cent nor more than 23.5 per cent, calculated to the dried substance.

BISMUTH SODIUM TARTRATE.—A basic bismuth sodium tartrate containing 72.9 to 73.7 per cent of bismuth.

Bismuth sodium tartrate is a finely divided, white powder, odorless and tasteless, permanent in air. The product is soluble in about three parts of water, except for a slight residue (0.1 per cent); the residue is soluble in sodium hydroxide T.S. The aqueous solution is alkaline to litmus paper. When acid is added gradually to an aqueous solution of bismuth sodium tartrate a precipitate is produced, which dissolves on the gradual addition of an alkali.

Dissolve 0.5 Gm. of bismuth sodium tartrate in 25 cc. of water; heat to 50 C; add 1.5 Gm. of sodium hydrosulfite dissolved in 5 cc. of 10 per cent diluted ammonia solution; a precipitate of metallic bismuth forms. To about 2 cc. of an aqueous solution (10 per cent) add a few drops of cupric sulfate T.S. A blue precipitate is formed, which is soluble in potassium hydroxide T.S. On standing, the alkaline solution gradually deposits a precipitate. Ignite 3 Gm. in a quartz crucible, cool, and cautiously add drop by drop just sufficient nitric acid to dissolve the residue when it is warmed; pour the acid solution into 100 cc. of water, evaporate the filtrate on the water bath to 30 cc., again filter and divide the filtrate into 5 cc. portions. To one portion add an equal volume of diluted sulfuric acid: the liquid does not become cloudy (lead). Add an excess of diluted ammonia solution to another portion: the supernatant liquid does not exhibit a bluish tint (copper). Add to another portion diluted hydrochloric acid: a precipitate, insoluble in an excess of hydrochloric acid and soluble in diluted ammonia solution, is not formed (silver). Ignite 1 Gm. in a quartz crucible; the residue meets the requirements of the U. S. P. test for arsenic.

Dry about 1 Gm. of bismuth sodium tartrate, weighed accurately.

at 100 C. to constant weight; the loss is from 2.6 to 3.6 per cent. Dissolve about 0.5 gm. of bismuth sodium tartrate accurately weighed in 20 to 30 cc. of water and add sufficient hydrochloric acid to redissolve the precipitate first formed; saturate the solution with hydrogen sulfide; collect the precipitate of bismuth sulfide; wash it successively with water, alcohol, carbon disulfide and ether and dry it at 100 C. the weight of bismuth sulfide is equivalent to not less than 72.7 nor more than 73.9 per cent of bismuth (R).

Colts	reaction	rod ct	differ	proxi
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D-smuth sodium thio glycollate occurs as a canary yellow hygroscopic, noncrystalline but granular substance possessing a garlic like odor. It is freely soluble in water but the solutions are not stable.

Add 1 drop of dilute hydrochloric acid to 1 cc of a 2 per cent solution of bismuth sodium thioglycollate solution; a heavy yellow precipitate separates that dissolves on the addition of another drop of acid. Add several drops of 36 per cent acetic acid to 1 cc of a 2 per cent solution of bismuth sodium thioglycollate; no precipitate forms. Add 3 drops of diluted ammoniacal solution to 1 cc of a 2 per cent solution; a slight change of color and a slight precipitate occurs within one-half hour. Add 1 drop of sodium hydroxide T.S. to 1 cc of 2 per cent solution of bismuth sodium thioglycollate; a precipitate forms, insoluble in excess of ammonia. To 1 cc of a 2 per cent solution of bismuth sodium thioglycollate add 1 drop of 0.5 per cent cupric sulfate solution; a precipitate forms that gives a blue coloration. The precipitate dissolves in dilute nitric acid. To 1 cc of a 2 per cent solution of bismuth sodium thioglycollate add 1 drop of 0.5 per cent ferric chloride solution; a precipitate forms which is soluble in dilute hydrochloric acid. To 1 cc of a 2 per cent solution of bismuth sodium thioglycollate add 1 drop of 0.5 per cent lead acetate paper.

Extract 0.2 Gm. of bismuth sublimed thioglycollate with 10 cc. of chloroform or ether; no residue remains after the evaporation of the solvent (free thioglycollate test). To 1 cc. of 2 per cent solution of bismuth sublimed thioglycollate add sufficient diluted hydrochloric acid to just dissolve the precipitate first formed and add several drops of barium chloride T.S. ■ precipitate does not appear.

Heat an accurately weighed sample of bismuth sodium thoglycolate weighing about 1 Gm in a 100° C oven for one hour cool in a desiccator and weigh the sample does not lose more than 3 per cent in weight. Transfer an accurately weighed sample of bismuth sodium thoglycolate weighing about 0.4 Gm to an Erlenmeyer flask dissolve in 100 cc. of water add enough diluted hydrochloric acid just to dissolve the precipitate first formed and saturate with hydrogen sulfide until the bismuth is completely precipitated as bismuth sulfide. Collect the precipitate in a prepared Gooch crucible wash with water alcohol ether chloroform and ether in the order named dry at 100° C cool in a desiccator and weigh the bismuth calculated from the bismuth sulfide is equivalent to not less than 37 per cent nor more than 39.5 per cent is the original calculated to the dry substance. Evaporate the filtrate from the bismuth determination to a small bulk transfer to a platinum dish add sulfuric acid and evaporate to dryness add a few drops of sulfuric acid evaporate to dryness again volatilize a small amount of ammonium carbonate from the dish cool in a desiccator and weigh the sodium calculated from the weight of sodium sulfate is not less than 12.23 per cent nor more than 13.04 per cent in the original substance calculated to the dry substance.

BISMUTH SODIUM TRIGLYCOLLAMATE.— $C_{24}H_{28}O_{25}N_4BiNa_7$.—F. W. 1142.—A double salt of bismuthyl sodium triglycollamate and disodium triglycollamate containing approximately 18.3 per cent of bismuth.

Bismuth sodium triglycollamate occurs as a white, odorless, crystalline powder with a somewhat salty taste. It is stable on exposure to air and is unaffected by light. It is very soluble in water but insoluble in organic solvents such as acetone, benzene and ether. The pH of a 2 per cent aqueous solution is between 7 and 8.

Add a drop of diluted hydrochloric acid to 0.1 Gm. of bismuth sodium triglycollamate; no effervescence occurs (carbonate). On a gram of bismuth sodium triglycollamate, 10 cc. of 10% sodium hydroxide solution is required for neutralization.

Ignite 3 Gm. of bismuth sodium triglycollamate in a crucible, not above 700° C. The residue is dissolved in 100 cc. of water. Add 100 cc. of 10% sodium hydroxide solution. The mixture is stirred and the crucible is washed with water. The crystalline precipitate on a filter is washed with water. The melting point of the washed, crystalline product, accurately weighed, in 50 cc. of hot water, add 2 drops of phenolphthalein T.S., and titrate with twentieth-normal sodium hydroxide. The neutralization equivalent should be not less than 94 nor more than 97.

Add 5 drops of barium chloride T.S. to 5 cc. of the filtrate the solution shows no more sulfate than corresponds to 0.25 cc. of fiftieth-normal sulfuric acid.

To another 5 cc. portion of the filtrate add an equal amount of sulfuric acid (caution!) and cool the mixture. Superimpose ferrous sulfate T.S.: no brown ring is produced at the junction of the two liquids (nitrate).

Ignite 3 Gm. of bismuth sodium triglycollamate in a crucible, not above 700° C. The residue is dissolved in 100 cc. of water. Add 100 cc. of 10% sodium hydroxide solution. The mixture is stirred and the crucible is washed with water. The crystalline precipitate on a filter is washed with water. The melting point of the washed, crystalline product, accurately weighed, in 50 cc. of hot water, add 2 drops of phenolphthalein T.S., and titrate with twentieth-normal sodium hydroxide. The neutralization equivalent should be not less than 94 nor more than 97.

Mix 0.2 Gm. of bismuth sodium triglycollamate with 2 cc. of sulfuric acid. Heat the mixture until fumes of sulfur trioxide are evolved. Cool and dilute with water until the solution measures 5 cc. This solution meets the requirements of the test for arsenic (U. S. P. XIII, p. 618).

Dry about 1.2 Gm. of bismuth sodium triglycollamate, accurately weighed, at 100° C. for two hours; the loss in weight does not exceed 2 per cent.

Ignite about 1 Gm. of dried bismuth sodium triglycollamate, accurately weighed, in a shallow porcelain crucible in a muffle furnace at 700° C. Cool, dissolve the residue with 5 cc. of hydrochloric acid, and transfer the solution quantitatively to a 250 cc. beaker with 100 cc. of water, heat to boiling and saturate the solution with hydrogen sulfide. Collect the precipitate on a tared Jena or Gooch crucible, and wash it successively with water, alcohol, ether, carbon disulfide, alcohol and ether. Dry the residue to constant weight at 100° C., cool and weigh, the bismuth content calculated from the weight of bismuth sulfide obtained is not less than 18 nor more than 19 per cent.

BISMUTH TRIBROMOPHENATE.—A basic bismuth tribromophenate of variable composition

Bismuth tribromophenate is an amorphous, yellow powder, neutral to moistened litmus paper. It is only slightly soluble in water, alcohol, chloroform, liquid petrolatum, and vegetable oils. Alkalis and strong acid decompose it. It is stable at temperatures below 120° C.

Boil about 1 Gm. of the salt with 10 cc. of sodium hydroxide T.S.

filter the liquid and acidify the filtrate with sulfuric acid the white curdy precipitate produced, when washed and dried, melts from 90° to

of a mixture of equal volumes of hydrochloric acid and distilled water in a separatory funnel for one or two minutes. Draw off the aqueous portion and concentrate to about 4 cc., pour it into 100 cc. of distilled water, filter, evaporate the filtrate on the water bath to 30 cc., again filter and divide this filtrate into portions of 5 cc. each. Mix one portion with an equal volume of diluted sulfuric acid it does not become cloudy (lead). Treat another portion with a slight excess of diluted ammonia solution the supernatant liquid does not exhibit a bluish tint (copper) another portion is not immediately affected by barium nitrate T S (sulfate).

Heat gently a mixture of about 0.2 Gm. of bismuth tribromophenate with 5 cc. of potassium hydroxide T S and about 0.2 Gm. of aluminum

(carbonate)

To about 0.5 Gm. of bismuth tribromophenate, accurately weighed add 20 cc. of hydrochloric acid and digest on a water bath. Add 150 cc. of water and filter. Rinse the beaker with 30 cc. of acidulated water and allow the washings to run through the filter. Saturate the combined filtrate and washings with hydrogen sulfide (care being exercised that the solution is not too acid so as to prevent quantitative precipitation of the bismuth sulfide) filter off the bismuth sulfide wash and dissolve in hot diluted nitric acid. Add a slight excess of diluted ammonia solution followed by 2 cc. of ammonium carbonate T S. Allow to stand 30 minutes filter off the precipitated bismuth hydroxide and heat to constant weight at dull red heat the residue of bismuth oxide (Bi_2O_3) should not be less than 45 per cent or more than 55 per cent of the original weight of bismuth tribromophenate taken corresponding to not less than 40 per cent nor more than 49 per cent of bismuth.

BRILLIANT GREEN.— $\text{C}_{21}\text{H}_{27}\text{N}_3\text{O}_4\text{S}$ —M W 482.54—Tetraethyldiaminotriphenylcarbinol anhydride sulfate.

Brilliant green occurs as an olive-green crystalline powder, soluble in water (1 Gm. in 20 cc.) and soluble in alcohol (1 Gm. in 20 cc.).

portion add several drops of sodium hydroxide T.S.: a brown to violet-brown precipitate forms. To another 10 cc. portion add 1 cc. of diluted hydrochloric acid and 1 cc. of barium chloride T.S.: a white precipitate results.

Dry an accurately weighed portion of brilliant green to constant weight at 110 C.: the loss in weight does not exceed 7.5 per cent. Ignite an accurately weighed specimen of brilliant green to constant weight: the residue is not more than 1 per cent.

Brilliant green meets the requirement limit for lead given under Methylrosanilin Chloride, U. S. P. XIII.

Dissolve 0.3 Gm. of brilliant green, accurately weighed, in 150 cc. of diluted alcohol and proceed as directed under "Assay," *National Formulary VIII*, p. 649: the amount of brilliant green found corresponds to not less than 95.0 per cent nor more than 101 per cent of the dried substance.

BROMISOVALUM.— $C_6H_{11}BrN_2O_2$.—M. W. 223.08.—2-Bromoisovalerylurea, obtained by the interaction of urea with bromoisovaleryl bromide.

Bromisovalum forms small, white, almost tasteless needles which are easily soluble in hot water, ether, alcohol and alkalis, but less readily soluble in cold water. It sublimes on heating and melts from 147° to 149° C.

Bromisovalum can be precipitated from a 10 per cent sodium hydroxide solution with acids. The presence of bromine may be demonstrated by fusion with sodium carbonate and potassium nitrate and testing for bromide with silver nitrate T.S. On heating an alcoholic solution of bromisovalum with sodium ethylate for several hours on the water bath, sodium bromide will precipitate. If this is filtered off and the filtrate evaporated, a crystalline mass remains which can be recrystallized from water. This is dimethylacrylic acid, melting at 230° C. If 1 Gm. of bromisovalum is boiled for about one minute with 10 per cent solution of sodium hydroxide, ammonia obtained from the urea will be given off. If the hot liquid is then cooled, acidified with nitric acid and extracted with ether, and the ether evaporated, an oily fluid, 1-bromoisovaleric acid, which has the specific odor of valeric acid, will remain. The biuret reaction cannot be obtained. On melting bromisovalum and adding concentrated sodium hydroxide solution and cupric sulfate T.S. no color reaction will take place.

BURBOT LIVER OIL. The oil extracted from the livers

Burbot liver oil is a pale, yellow, oily liquid. It has a slightly fishy but not rancid odor and a fishy taste. It is slightly soluble in alcohol but is soluble in ether, chloroform, benzene, carbon disulfide and ethyl acetate. The specific gravity is from 0.921 to 0.927 at 25 C. The refractive index is from 1.479 to 1.482 at 20° C.

A solution of one drop of the oil in 1 cc. of chloroform, when shaken with one drop of sulfuric acid, acquires a light violet color, changing to violet, dark green and finally brown. Treat 5 cc. of oil with 5 cc. of benzene and centrifuge for 25 minutes at 25° C.: no precipitate forms and a clear solution remains.

Fill a tall cylindric, standard oil sample bottle of about 120 cc. capacity with burbot liver oil at a temperature between 23 and 23 C., stopper, and immerse the bottle in a mixture of ice and distilled water for five hours: the oil remains fluid and forms no deposit.

Dissolve 2 Gm. of burbot liver oil, accurately weighed, in 20 cc. of a mixture of equal volumes of alcohol and ether, which previously has been neutralized with tenth-normal sodium hydroxide, using five drops of phenolphthalein T. S. as indicator, and titrate with tenth-normal sodium hydroxide to the production of a pink color which persists for fifteen seconds: not more than 1 cc. of tenth-normal sodium

hydroxide is required (*free acid*) The amount of unsaponifiable matter as determined by the method of *U. S. P. XIII*, p 643, is not less than 0.9 per cent nor more than 3.0 per cent The saponification value as determined by the method of *U. S. P. XIII*, p 647, is not less than 184 nor more than 196. The iodine value as determined by the method of *U. S. P. XIII*, p 647, on 0.18 to 0.20 Gm of sample, accurately weighed, is not less than 155 nor more than 180

BUTABARBITAL SODIUM.— $C_{10}H_{13}N_2O_3Na$.—M. W. 234.23.—Sodium 5-ethyl-5(1-methyl propyl) barbiturate.

Butabarbital sodium occurs as a white bitter-tasting powder. It is soluble in water (1 in 2) and in alcohol (1 in 67), practically insoluble in dry ether and in benzene. The pH of a 1 per cent solution is from 9.0 to 10.2.

Dissolve about 0.5 Gm of butabarbital sodium in 100 cc of water and acidify the solution with diluted hydrochloric acid. Allow the ethyl *sec* butyl barbituric acid to crystallize from solution, collect it on a filter, wash with water and dry at 100° C. the crystals melt at 165 to 169° C.

Incinerate about 0.1 Gm of butabarbital sodium the residue responds to tests for sodium carbonate. Dissolve about 0.3 Gm of butabarbital sodium in 10 cc of water and divide into two portions. To one portion add 1 cc of mercuric bichloride TS a white precipitate results, soluble in an excess of strong ammonia solution. To the other portion add 5 cc. of silver nitrate TS a white precipitate results, soluble in an excess of strong ammonia solution.

Dissolve about 0.5 Gm of butabarbital sodium in 5 cc. of sulfuric

Dry about 10 Gm. of butabarbital sodium, accurately weighed, at 100° C for 20 hours the loss in weight is not more than 5 per cent.

Dissolve about 0.5 Gm. of butabarbital sodium, accurately weighed, in 10 cc of water in a separatory funnel, add to the solution 15 cc of diluted hydrochloric acid and extract the liberated butabarbital with eight successive portions of ether, using 25 cc., 20 cc., 20 cc., 10 cc.,

BUTALLYLONAL.— $C_{11}H_{15}BrN_2O_3$.—M. W. 303.16.—5-*sec* butyl 5 β bromoallyl barbituric acid

Butallylonal occurs as a fine, white, crystalline powder, with a slightly bitter taste. It is completely soluble in alcohol and ether, very slightly soluble in cold water and insoluble in the paraffin hydrocarbons. A saturated aqueous solution is acid to litmus paper. Butallylonal melts at 130° to 135° C.

Place approximately 1 Gm. of butallylonal in a 25 cc. glass stoppered cylinder, add 10 cc of water and 1 cc. of sodium hydroxide TS and shake for one minute, filter through paper and divide into two portions,

to one portion add 1 cc. of mercuric bichloride T.S.: a white precipitate results, soluble in 10 cc. of diluted ammonia solution. To the other portion add 5 cc. of silver nitrate T.S.: a white precipitate results, soluble in 5 cc. of diluted ammonia solution.

Fuse about 0.1 Gm. of butallylonal and 1 Gm. of crushed potassium hydroxide, previously moistened with 1 cc. of alcoholic potassium hydroxide solution, in a nickel crucible: it is decomposed with the evolution of ammonia; cool, dissolve the residue in 10 cc. of water, add 10 cc. of diluted nitric acid, filter through paper; to the filtrate add 5 cc. of silver nitrate T.S.: a curdy dirty white precipitate results, soluble in excess of strong ammonia solution.

Dissolve 0.1 Gm. of butallylonal in 1 cc. of sulfuric acid: the liquid assumes a yellow color, changing slowly to a brownish red, finally to a dark red. Place 1 Gm. of butallylonal in a 25 cc. glass stoppered cylinder, add 10 cc. of water, shake for one minute, filter through paper and divide into two portions. To one portion add 0.5 cc. of bromine T.S.: an immediate discoloration occurs. To the other portion add 0.1 cc. of tenth-normal potassium permanganate: a yellow color appears immediately.

Boil 0.5 Gm. of butallylonal with 50 cc. of water for two minutes: no odor develops; cool and filter, separate portions of 10 cc. each of the filtrate, to one add 1 cc. of dilute sodium hydroxide solution and 1 cc. of dilute nitric acid, to the other add 1 cc. of dilute sodium hydroxide solution or precipitate.

To the residue on about 0.25

BUTAMBEN PICRATE. — $C_{28}H_{33}N_5O_{11}$. — F. W. 615.59. — A compound consisting of one molecule of trinitrophenol (picric acid) and two molecules of the normal butyl ester of 4-aminobenzoic acid.

Butamben picrate is a yellow, odorless, amorphous powder, with a slightly bitter taste. One part of butamben picrate is soluble in 2,000 parts of water, and in 100 parts of cottonseed oil; it is soluble in alcohol, chloroform, ether and benzene. It melts at 109° to 110° C.

The aqueous solution of butamben picrate is greenish yellow; the color is intensified by the addition of alkali and is decreased by acid. A saturated aqueous solution of butamben picrate is not affected by the addition of mercuric potassium iodide T.S., of silver nitrate T.S. or of hydrogen sulfide solution. A few drops of saturated solution of sodium nitrite added to the acidulated solution of butamben picrate and followed by a few drops of a slightly alkaline solution of betanaphthol produces a salmon colored precipitate which quickly darkens. A purplish-red color is produced if a 1 per cent potassium cyanide solution be added to an aqueous solution of butamben picrate.

Incinerate 0.5 Gm. of butamben picrate, accurately weighed: the ash does not exceed 0.1 per cent.

BUTETHAL. — $C_{10}H_{16}N_2O_3$ — M. W. 212.24 — 5-n-Butyl-5-ethylbarbituric acid.

Butethal occurs as a white, crystalline, odorless powder, with a slightly bitter taste. It is readily soluble in alcohol, about 1 in 5, and ether, about 1 in 10; very slightly soluble in cold water; and insoluble in the paraffin hydrocarbons. A saturated aqueous solution is acid to litmus paper. Butethal melts at $124-127^{\circ}$ C. It is stable in air.

Place 0.3 Gm. in a 25 cc. glass stoppered cylinder, add a mixture of 1 cc. sodium hydroxide T.S. and 5 cc. of water, shake the contents for one minute, filter through paper and divide into two portions. To one portion add 1 cc. of mercuric bichloride T.S. a white precipitate results, soluble in 10 cc. of diluted ammonia solution. To the other portion add 5 cc. of silver nitrate T.S. a white precipitate results, soluble in 5 cc. of diluted ammonia solution. Boil 0.5 Gm. with 5 cc. of a 25 per cent sodium hydroxide solution it is decomposed with the evolution of ammonia.

Dissolve 0.1 Gm. in 1 cc. of sulfuric acid the solution is colorless (*readily carbonizable substances*). Boil 0.5 Gm. with 50 cc. water for two minutes no odor develops, cool and filter separate portions of 10 cc. each of the filtrate yield no opalescence with 1 cc. of diluted nitric acid and 1 cc. of silver nitrate T.S. (*chloride*), and no turbidity with 1 cc. of diluted nitric acid and 1 cc. of barium nitrate T.S. (*sulfate*), no color or precipitate on saturation with hydrogen sulfide (*salts of heavy metals*).

Ignite about 1 Gm., accurately weighed the residue does not exceed 0.1 per cent.

Dissolve about 0.5 Gm., accurately weighed, in 25 cc. of previously neutralized alcohol dilute with an equal volume of water and titrate with tenth normal sodium hydroxide using thymolphthalein T.S. as an indicator the amount of tenth normal sodium hydroxide consumed corresponds to not less than 98.5 per cent nor more than 101.5 per cent of butylethyl barbituric acid.

BUTETHAMINE FORMATE — $C_{14}H_{22}N_2O_4$ — M. W. 282.34 — 2-Isobutylaminoethyl *p* aminobenzoate formate.

Evaporate the chloroform layer from the foregoing extraction to dry.

Accurately weigh about 0.2 Gm. of butethamine formate. Dry over phosphorus pentoxide in a vacuum desiccator the loss in weight is not more than 0.5 per cent. Ash about 0.2 Gm. of Monocaine Formate, accurately weighed the ash content is not more than 0.15 per cent.

Transfer 0.15 Gm. of butethamine formate, accurately weighed, to a

plete solution. Add 10 cc. of tenth-normal hydrochloric acid and 2 cc. of methyl red T.S. 10 cc. of water and hydroxide. Each cc. of 0.02723 Gm. of butethamine formate the amount of butethamine formate found is not less than 95.0 per cent.

Decant the residual aqueous layer in the separatory funnel into a 250 cc. beaker. Wash the funnel with two 20 cc. portions of water and add the washings to the original solution. To the combined mixture add 1 Gm. of sodium carbonate and dilute the solution with water to approximately 100 cc. Evaporate the solution to about 50 cc. by gentle boiling. Titrate 25 cc. of tenth-normal potassium permanganate into the hot solution. Carefully acidify (caution) the solution with concentrated sulfuric acid. Clear the solution by titration with 15 cc. of tenth-normal oxalic acid and finally titrate the excess oxalic acid with more of the tenth-normal potassium permanganate. The difference between the total volumes of potassium permanganate and oxalic acid is due to the oxidation of formic acid. One cc. of tenth-normal potassium permanganate is equivalent to 0.002101 Gm. of formic acid; the amount of formic acid found is not less than 15.3 per cent nor more than 16.8 per cent of the weight taken.

BUTETHAMINE HYDROCHLORIDE.— $C_{13}H_{20}N_2 \cdot HCl$.—M. W. 272.78.—2-Isobutylaminoethyl *p*-aminobenzoate hydrochloride.

Butetha possessing a the range alcohol an soluble in e within the range 1 to 47.

Dissolve 1 cc. of precipitate 5 cc. port 0.5 cc. of ammonia itate form iodide T precipitate forms. Add a white another acid and diluted precip- tassium a white

Dissolve 0.1 Gm. of butethamine hydrochloride in 5 cc. of water. Add two drops of sulfuric acid and 1 cc. of a saturated solution of sodium nitrite; heat to 50° C.; a yellow emulsion forms. Continue heating; an orange-red solution results, and reddish oil droplets form on the bottom of the tube and in the froth.

Weigh accurately about 0.5 Gm. of butethamine hydrochloride. Dry at 100° C. for 2 hours. Ash cent. 1.0. Chloride silver precipitate than

Transfer about 0.15 Gm. of butethamine hydrochloride, accurately weighed, to a separatory funnel and proceed according to the method described for procaine hydrochloride in the book *Methods of Analysis of the Association of Official Agricultural Chemists*, ed. 6, p. 667, Method II. Each cubic centimeter of tenth-normal hydrochloric acid is equivalent to 0.02723 Gm. of butethamine hydrochloride; the butethamine hydrochloride content is not less than 95 per cent nor more than 105 per cent.

$C_4H_7Cl_3O_2$ —M. W. Chloral Hydrate.—

orthorhombic laminae, acid, nauseous taste.

It fuses at about 78° C. to a transparent liquid, which, on cooling, begins to solidify at about 71° C. It is soluble in about 50 parts of water, and in its own weight of glycerin or of alcohol (90 per cent). It slowly dissolves in 20 parts of chloroform. From a solution in alcohol, it is precipitated by the gradual addition of water in the form of globules said to consist of butylchloral alcoholate $C_4H_9Cl_2O$. C_4H_9OCl . The alcoholic solution is neutral, and the aqueous solution is neutral or but slightly acid to litmus.

It gives no precipitate with silver nitrate T.S. Heat about 0.2 Gm. of butylchloral hydrate with 10 cc. of sodium hydroxide T.S. and add 2 drops of a saturated aqueous solution of aniline the odor of phenyl isocyanide cannot be detected (chloral hydrate).

CETYL PYRIDINIUM CHLORIDE — $C_{21}H_{40}ClNO$ — M. W. 357.99 — The monohydrate of the quaternary salt of pyridine and cetyl chloride

Cetyl pyridinium chloride occurs as a white powder possessing a slight odor. It melts within the range 77-83° C. It is very soluble in alcohol, chloroform and water and only very slightly soluble in benzene and in ether. The pH of a 1 per cent aqueous solution is 6.0 to 7.0 as determined by the use of indicators (glass electrode instruments give variable results). The surface tension at 25° C. of a 0.1 per cent aqueous solution is about 43.00 of a 1.0 per cent aqueous solution, about 41.40, and of a 10 per cent aqueous solution about 38.15.

Dissolve 0.1 Gm. of cetyl pyridinium chloride in 50 cc. of water. Add 1 cc. of silver nitrate T.S. to a 5 cc. portion of the solution a white precipitate forms which is soluble in strong ammonia solution.

Add 5 cc. of about one hundredth molar potassium ferricyanide to 5 cc. of the cetyl pyridinium chloride solution a yellow precipitate forms. Add 1 cc. of a saturated potassium thiocyanate solution to a 1 cc. portion of the cetyl pyridinium chloride solution a white gelatinous precipitate forms. Add 1 cc. of saturated picric acid solution to 1 cc. of the cetyl pyridinium chloride solution a yellow precipitate forms.

Heat gently about 0.25 Gm. of cetyl pyridinium chloride contained in a test tube until the substance melts and a brown color develops the odor of pyridine is readily detected.

Weigh accurately about 0.5 Gm. of cetyl pyridinium chloride. Dry to constant weight in a vacuum over phosphorous pentoxide the loss in weight is not less than 4.5 per cent nor more than 5.5 per cent. Ash the dried sample the weight of the residue is not more than 0.2 per cent.

Weigh accurately about 0.25 Gm. of cetyl pyridinium chloride. Transfer to a 100 cc. volumetric flask. Add 5 cc. of buffer solution (260 Gm. of sodium acetate and 250 cc. of 36 per cent acetic acid mixed with water to make 1 liter). Add 50 cc. of one hundredth molar potassium ferricyanide. Dilute to the mark with water mix allow to stand one hour and filter discarding the first 15 cc. of the filtrate. Add 5 cc. of 10 per cent potassium iodide solution to a 50 cc. aliquot of the filtrate in an iodine flask. Add 10 cc. of concentrated hydrochloric acid and allow to stand for one minute. Add 10 cc. of 10 per cent zinc sulfate solution and titrate with one hundredth normal sodium thiosulfate using starch T.S. near the end of the titration. Each cc. of one hundredth normal sodium thiosulfate is equivalent to 0.01074 Gm. of cetyl pyridinium chloride monohydrate the cetyl pyridinium chloride monohydrate content is not less than 97 per cent nor more than 103 per cent.

CHLORGUANIDE HYDROCHLORIDE — $C_{11}H_{16}N_5ClHCl$ — M. W. 290.2 — N^1 (p chlorophenyl) N^5 isopropylguanide hydrochloride

Chlorguanide hydrochloride occurs as odorless colorless fine crystals or as a crystalline powder possessing a bitter taste. It is soluble in alcohol, slightly soluble in water and practically insoluble in chloroform and in ether. The pH of a filtered saturated solution is between 5.8 and 6.3. Chlorguanide hydrochloride melts between 248° and 252° C. It exhibits

an ultraviolet absorption maximum at 2590 Å., when dissolved in alcohol ($E_{1\text{ cm.}}^{1\%} = 690 \pm 7$).

Prepare 50 cc. of a saturated solution of chlorguanide hydrochloride in water and divide into five portions in separate test tubes. To one portion add 1 cc. of diluted nitric acid and 1 cc. of silver nitrate T.S.: a white precipitate forms. To another portion add 5 drops of iodine T.S.: an orange-brown precipitate forms. To another portion add 5 drops of potassium ferrocyanide T.S., rendered slightly acid to litmus with diluted nitric acid: a white precipitate forms which is soluble on addition of a few drops of diluted nitric acid. To another portion add 5 drops of a slightly acid solution of potassium dichromate T.S.: a yellow precipitate forms which is soluble in a few drops of diluted nitric acid. To another portion add bromine T.S., dropwise: a yellow precipitate forms which immediately redissolves on mixing; on addition of an excess of bromine T.S., a permanent orange precipitate forms.

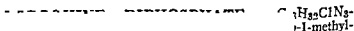
Dissolve about 0.1 Gm. of chlorguanide hydrochloride in 25 cc. of water in a separatory funnel and add 10 cc. of tenth-normal sodium hydroxide. Extract the precipitated chlorguanide base with 25 cc. of ether. Separate, filter the ether extract, evaporate nearly to dryness, and dry the residue at 100° C.: the residue melts between 130° and 135° C.

Dry about 1 Gm. of chlorguanide hydrochloride, accurately weighed, at 100° C. for three hours: the loss in weight is not more than 0.3 per cent. Ash about 0.5 Gm. of chlorguanide hydrochloride, accurately weighed, in the presence of sulfuric acid: the residue is not more than 0.1 per cent.

Transfer about 0.2 Gm. of chlorguanide hydrochloride to an Erlenmeyer flask, add 50 cc. of water and dissolve the solid. Add 1 cc. of nitric acid and exactly 40 cc. of fiftieth-normal silver nitrate. Add 3-5 cc. of nitrobenzene and swirl the flask to entrap the precipitated silver chloride. Add 3 cc. of ferric ammonium sulfate T.S., and titrate with fiftieth-normal ammonium thiocyanate. Each cc. of fiftieth-normal silver nitrate is equivalent to 0.000709 Gm. of chlorine. The readily ionizable chloride is not less than 11.5 per cent nor more than 12.3 per cent, calculated to the dry substance.

Determine the nitrogen content of chlorguanide hydrochloride by the Kjeldahl method: the nitrogen content is not less than 23.5 per cent nor more than 24.5 per cent, calculated to the dry substance.

Transfer	about 0.2 Gm.	of chlorguanide hydrochloride	to a separatory
funnel,			funnel.
the precipitate			hydroxide T.S. Extract
10 cc.			with 30 cc., 25 cc., 10 cc.,
with 10			the ether extracts, wash
pledget.			thoroughly with a cotton
stream of			water, and filter using a
of the			or one hour: the weight
cent, calculated			is not more than 89.2 per



Chloroquine diphosphate occurs as a white, crystalline powder, possessing a bitter taste. It melts in the range 193-195° C. Two modifications of chloroquine diphosphate are obtainable. The second form melts at 215-218° C. It is freely soluble in water; and practically insoluble in alcohol, benzene, chloroform, and ether. The pH of a 1 per cent solution in water is about 4.5.

Dissolve about 50 mg. of chloroquine diphosphate in 3 cc. of water. Add a few drops of ammonium molybdate T.S.: a white precipitate develops immediately.

Dissolve 20 mg. of chloroquine diphosphate in 20 cc. of water. Add 5 cc. of a saturated aqueous solution of picric acid: a yellow precipitate forms immediately. Filter off the precipitate, wash with water and air-dry on the filter funnel: the product melts from 205-210° C. (Caution!).

Dissolve 0.25 Gm. of chloroquine diphosphate in 50 cc. of water.

Add 1 cc of strong ammonia solution and extract with two 30 cc portions of cyclohexane. Evaporate the cyclohexane solution to dryness on the steam bath. Place the residual oil in a vacuum desiccator over phosphorus pentoxide and allow to stand over night to permit crystallization; the solid material melts at a temperature of 87-90° C.

Dry about 0.25 Gm. of chloroquine diphosphate, accurately weighed,

and ten tablets in a mortar and pestle. Add 100 cc of a 1 per cent solution of the choline salt to 2 cc of cobaltous chloride solution (U. S. P. test solution diluted 1 to 25). Add 2 cc of 2 per cent potassium ferrocyanide solution; an emerald green color develops immediately. Add 0.2 cc of mercuric sulfate T. S. to 2 cc of a 10 per cent solution of choline dihydrogen citrate. Heat the mixture to boiling and then add 5 drops of potassium permanganate T. S.; a precipitate develops with a slight yellow color. Dissolve 0.5 Gm. of choline dihydrogen citrate in 2 cc of water. Add the choline solution to 3 cc of a saturated picric acid solution. Allow the aqueous solution to evaporate slowly. Filter off the crystalline material and wash thoroughly with ether; the crystals melt from 245-251° C. (Caution!) with considerable decomposition. Dissolve 0.5 Gm. of choline dihydrogen citrate in 2 cc of water. Add to 1 cc of the choline solution a few drops of phosphotungstic acid T. S.; a white curdy precipitate occurs. Add to another 1 cc portion of the choline solution a few drops of tannic acid T. S.; no precipitate should form.

Dry about 0.5 Gm. of choline dihydrogen citrate, accurately weighed,

in vacuum over phosphorus pentoxide for 24 hours; the loss in weight does not exceed 0.25 per cent. Ash about 0.5 Gm. of choline dihydrogen citrate, accurately weighed; the residue does not exceed 0.05 per cent.

CHOLINE DIHYDROGEN CITRATE— $C_{11}H_{21}NO_8$ —*M. W. 295.29*—Trimethylhydroxyethylammonium citrate—The dihydrogen citrate of trimethyl ethanolammonium hydroxide.

Choline dihydrogen citrate occurs as a white, crystalline, granular substance, possessing an acid taste. It melts at 105-107.5° C. It is freely soluble in water, very slightly soluble in alcohol, and practically insoluble in benzene, in chloroform, and in ether. The p*H* of a 25 per cent solution is about 4.25.

Add 1 cc of a 1 per cent solution of the choline salt to 2 cc of cobaltous chloride solution (U. S. P. test solution diluted 1 to 25). Add 2 cc of 2 per cent potassium ferrocyanide solution; an emerald green color develops immediately.

Add 0.2 cc of mercuric sulfate T. S. to 2 cc of a 10 per cent solution of choline dihydrogen citrate. Heat the mixture to boiling and then add 5 drops of potassium permanganate T. S.; a precipitate develops with a slight yellow color.

Dissolve 0.5 Gm. of choline dihydrogen citrate in 2 cc of water. Add the choline solution to 3 cc of a saturated picric acid solution. Allow the aqueous solution to evaporate slowly. Filter off the crystalline material and wash thoroughly with ether; the crystals melt from 245-251° C. (Caution!) with considerable decomposition.

Dissolve 0.5 Gm. of choline dihydrogen citrate in 2 cc of water. Add to 1 cc of the choline solution a few drops of phosphotungstic acid T. S.; a white curdy precipitate occurs. Add to another 1 cc portion of the choline solution a few drops of tannic acid T. S.; no precipitate should form.

Dry about 0.5 Gm. of choline dihydrogen citrate, accurately weighed, in vacuum over phosphorus pentoxide for 24 hours; the loss in weight does not exceed 0.25 per cent. Ash about 0.5 Gm. of choline dihydrogen citrate, accurately weighed; the residue does not exceed 0.05 per cent.

Weigh, accurately, about 0.2 Gm. of choline chloride, U. S. P. Reference Standard previously dried at 110° C. for 4 hours, and dilute to 100 cc. with water in a volumetric flask. Weigh, accurately, about 0.45 Gm. of choline dihydrogen citrate and dilute to 100 cc. with water in a volumetric flask. Transfer 0.5, 1.5, 2.5, 4.0, and 5.0 cc. respectively, of the standard solution to five conical 15 cc. centrifuge tubes. Transfer 1.5 cc. and 4.0 cc. of the test solution to two additional centrifuge tubes. Add 1.4 cc. of 6 normal hydrochloric acid to each tube and dilute to 7 cc. with water. Dissolve 2.0 Gm. of ammonium reineckate (U. S. P. XIII, p. 741) in 100 cc. of 1.2 normal tube, slowly, with stand 30 minutes, with minutes at 2500 r.p.m. and carefully wipe the 3 cc. of cooled 1.2 normal hydrochloric acid by pouring it into the centrifuge tube down the stirring rod previously used. Stir the precipitate gently but avoid prolonged stirring. Centrifuge for 15 minutes at 2500 r.p.m., and again discard the supernatant liquid. Dissolve the precipitate of choline reineckate in 2 cc. of acetone and transfer the solution to a 10 cc. volumetric flask. Wash each centrifuge tube twice more with 2 cc. portions of acetone and transfer the washings to the volumetric flask. Dilute the contents of the flasks to the mark with acetone and read the light absorption on a spectrophotometer at 5260 Å. Establish a standard curve from the values obtained from the standard solutions. Obtain the choline chloride equivalents of the test solutions by referring their absorption values to the standard curve: each mg. of choline chloride is equivalent to 0.0021152 Gm. of choline dihydrogen citrate. The choline dihydrogen citrate concentration is not less than 98 nor more than 102 per cent.

CHOLINE DIHYDROGEN CITRATE SYRUP: Transfer 5 cc. of the choline dihydrogen citrate syrup to a 250 cc. volumetric flask, using a pipette calibrated to contain. Wash out the syrup from the pipette with water, transfer the washings into the flask and dilute to 250 cc. Mix, and transfer 1.5 cc. and 3.0 cc. to two centrifuge tubes. Add 1.4 cc. of 6 normal hydrochloric acid to each tube and continue the assay as described above: the choline content is not less than 90 per cent nor more than 110 per cent of the claimed amount.

CHONDODENDRON TOMENTOSUM EXTRACT, PURIFIED.—A curare preparation containing therapeutically desirable constituents of curare.

Dilute in a large Pyrex test tube 0.25 cc. of purified chondodendrum tomentosum extract with 25 cc. of distilled water and add 0.2 cc. of concentrated sulfuric acid and 2 cc. of 1 per cent potassium iodate solution. Mix and warm in a water bath at 50° C. for one-half hour. A yellow color is developed.

The physiologic activity of purified chondodendrum tomentosum extract is determined on rabbits: the provisional unit is equivalent to the potency of 0.15 mg. of d-tubocurarine chloride.

COPARAFFINATE.—A mixture of water insoluble isoparaffinic acids partially neutralized with iso-octyl hydroxy-benzyl-dialkyl amines.

Coparaffinate is a viscid, dark brown, oily liquid having a characteristic odor of burnt petroleum. It is immiscible with water; freely miscible with alcohol, volatile oil and fixed oil. The specific gravity is from 0.970 to 0.980 at 25 C.

Place cc. of paper methyl two drops of liquid in a 20 cc. graduated cylinder, add 20 med of add

meta-CRESYLACETATE.— $C_9H_{10}O_2$ —M. W. 150.17—

Meta-cresylacetate occurs as a colorless oily liquid, possessing a char-

acteristic odor. It is practically insoluble in water, but soluble in the ordinary organic solvents and in fixed and volatile oils. It is volatile with steam.

Shake 10 cc of *meta*-cresylacetate with 100 cc of water for one minute and filter through a wet filter, the filtrate has a neutral reaction and does not produce a violet color with ferric chloride TS or a turbidity with silver nitrate TS. Evaporate 10 cc of *meta*-cresylacetate in a tared porcelain dish and ignite the residue is negligible.

CYCLOBARBITAL.— $C_{12}H_{16}N_2O_3$ —M. W. 236.26—
5 Δ^1 -Cyclohexenyl-5-ethyl barbituric acid.

Cyclobarbitol occurs as a white, crystalline, odorless powder, with a bitter taste. It is readily soluble in alcohol, about 1 in 5, and ether, about 1 in 10 and more or less soluble in benzene and in chloroform. A saturated

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1 cc
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Ash about 1 Gm. accurately weighed there is not more than 0.01 per cent residue.

Dissolve about 0.5 Gm, accurately weighed, in 25 cc of previously neutralized alcohol, dilute with an equal volume of water and titrate with tenth normal sodium hydroxide, using thymolphthalein T.S. as an indicator the amount of tenth normal sodium hydroxide consumed corresponds to not less than 98.5 per cent nor more than 101.5 per cent of cyclobarbitol.

DEHYDROCHOLIC ACID.— $C_{24}H_{34}O_5$ —M. W. 402.51.
—An oxidation product of cholic acid derived from natural bile acids

Dehydrocholic acid occurs as a fine, colorless, crystalline powder with a bitter taste. It is sparingly soluble in alcohol and glacial acetic acid. It melts at 233-235°C.

Boil about 1 Gm. of dehydrocholic acid with 100 cc. of water for two minutes, no odor develops. Cool and filter. Separate portions of 10 cc. each of the filtrate as usual.

metals)

DIALLYLBARBITURIC ACID.— $C_{10}H_{12}N_2O_3$.—M. W. 208.21.

Diallylbarbituric acid occurs as a fine, white crystalline powder, with a slightly bitter taste. It is completely soluble in alcohol and ether; very slightly soluble in cold water; and insoluble in the paraffin hydrocarbons. A saturated aqueous solution is acid to litmus paper. Diallylbarbituric acid melts at 171-173° C.

Place approximately 0.3 Gm. diallylbarbituric acid in a 25 cc. glass stoppered cylinder, add a mixture of 1 cc. normal sodium hydroxide solution and 5 cc. of water, shake the contents for one minute, filter through paper and divide into two portions. To one portion add 1 cc. of mercuric bichloride T.S.: a white precipitate results, soluble in 10 cc. of diluted ammonia solution. To the other portion add 5 cc. of silver nitrate T.S.: a white precipitate results, soluble in 5 cc. of diluted ammonia solution. Boil 0.5 Gm. with 5 cc. of a 25 per cent sodium hydroxide solution: it is decomposed with the evolution of ammonia. Dissolve 0.1 Gm. in 1 cc. of sulfuric acid: the liquid assumes a yellow color, changing to a dark red. Place 1 Gm. in a test tube, add 10 cc. of water, shake for one minute into two portions; to one portion add a few drops of potassium permanganate T.S.: a yellow

acid with 50 cc. of water for two days, and filter. Separate portions of 10 cc.

each of the filtrate yield no opalescence with 1 cc. of diluted nitric acid and 1 cc. of silver nitrate T.S. (*chloride*); no turbidity with 1 cc. of diluted nitric acid and 1 cc. of barium nitrate T.S. (*sulfate*); no color or precipitate on saturation with hydrogen sulfide (*salts of heavy metals*).

a fine, white, crystalline, odorless, soluble in water, (about 2 in 1); freely soluble in alcohol and chloroform, slightly soluble in ether, warming, but with difficulty in the cold. It is faintly alkaline to litmus, produces a blue color on the tongue. Dibucaine hydrochloride

melts at 90 to 96° C.

Transfer about 0.5 Gm. of dibucaine hydrochloride to a suitable Squibb separatory funnel, add 25 cc. of water, followed by the addition of 2 cc. of normal sodium hydroxide solution and extract with three successive portions of purified petroleum benzene, using 25 cc., 20. and 10 cc., respectively; evaporate the combined petroleum benzene extracts to dryness; the crystals melt at not less than 64° C. Dibucaine base fluoresces with the more common oxygen containing acids. Dissolve about 0.5 Gm. of dibucaine hydrochloride in 50 cc. of water, add

1 cc. of 10 per cent sodium hydroxide solution, shake for one minute, filter, wash the filter with 5 cc. of water, and combine the filtrate and washings. To one portion add 1 cc. of mercuric bichloride T.S.: a white precipitate results, soluble in 10 cc. of diluted ammonia solution. To the other portion add 5 cc. of silver nitrate T.S.: a white precipitate results, soluble in 5 cc. of diluted ammonia solution. Boil 0.5 Gm. with 5 cc. of a 25 per cent sodium hydroxide solution: it is decomposed with the evolution of ammonia. Dissolve 0.1 Gm. in 1 cc. of sulfuric acid: the liquid assumes a yellow color, changing to a dark red. Place 1 Gm. in a test tube, add 10 cc. of water, shake for one minute into two portions; to one portion add a few drops of potassium permanganate T.S.: a yellow

acid with 50 cc. of water for two days, and filter. Separate portions of 10 cc. each of the filtrate yield no opalescence with 1 cc. of diluted nitric acid and 1 cc. of silver nitrate T.S. (*chloride*); no turbidity with 1 cc. of diluted nitric acid and 1 cc. of barium nitrate T.S. (*sulfate*); no color or precipitate on saturation with hydrogen sulfide (*salts of heavy metals*).

Dry about 0.5 Gm of dibenzoin hydrochloride, accurately weighed, over sulfuric acid in a desiccator for 48 hours. The loss does not exceed 2.5 per cent. Incinerate about 0.5 Gm., accurately weighed; the residue is not more than 0.1 per cent. Transfer about 0.5 Gm. to a 40 cc beaker, add 25 cc of water, followed by the addition of 25 cc. of silver nitrate TS and 5 cc. of nitric acid, subsequently boil, with continuous stirring and allow to cool in a dark place. Collect the precipitate of silver chloride in a Gooch crucible, wash with diluted nitric acid followed by alcohol and ether. Finally dry to constant weight at 105°C. The amount of hydrogen chloride calculated from the silver chloride found corresponds to not less than 9.5 per cent nor more than 9.7 per cent calculated to the dried substance. Transfer about 0.5 Gm. accurately weighed to a suitable Soxhlet separatory funnel add 10 cc of water followed by the addition of 2 cc. of sodium hydroxide TS, extract with six successive portions of chloroform, using 50 cc., 25 cc., 20 cc., 15 cc., 10 cc. and 10 cc., respectively wash the combined chloroform solution with 15 cc of water and evaporate to a thick oil in a stream of warm air, dry over sulfuric acid in a partially exhausted desiccator dissolve the oily residue in about 10 cc of previously neutralized alcohol warm slightly add 10 cc of tenth normal hydrochloric acid a titration followed by the addition of an equal volume of water. Determine the excess of acid by titration with fifth normal sodium hydroxide solution using methyl red TS. as an indicator. The amount of tenth normal hydrochloric acid solution consumed corresponds to not less than 88.5 per cent nor more than 90.5 per cent butoxyethylaminomethyl amide of quinoline carboxylic acid calculated to the dried substance.

DICUMAROL— $C_{12}H_{12}O_6$ —M W 336.29—3,3 Methylenebis(4 hydroxycoumarin)

Dicumarol occurs as a white or slightly buff colored crystalline powder. It melts in the range 247-291°C. It is soluble in aqueous alkalis and pyridine slightly soluble in benzene and chloroform and practically insoluble in water alcohol and ether.

Dissolve 0.1 Gm of Dicumarol in 10 cc of sodium hydroxide TS. and allow the solution to stand. It gradually darkens to a deep brown color. Cool and add 2 drops of silver nitrate TS. The product melts

at 247-291°C. Add 2 drops of silver nitrate TS. No precipitate

Add 1 drop of ferric chloride TS to the remaining 5 cc of filtrate. No color develops (absence of salicylates and 4 hydroxycoumarin).

Dissolve 1 Gm of Dicumarol in enough sodium hydroxide TS to give complete solution, and dilute to 20 cc with water. Add 5 drops of sodium sulfide TS. No more turbidity develops than corresponds to 50 ppm of lead (USP XVII).

Dry 0.5 Gm of Dicumarol accurately weighed for two hours at 100°C. The loss in weight does not exceed 0.5 per cent.

Ash about 0.2 Gm of Dicumarol accurately weighed. The amount of residue is negligible.

Transfer about 0.5 Gm of Dicumarol accurately weighed to a 100 cc

DIENESTROL— $C_{18}H_{18}O_2$ —M W 266.32—3,4 bis (p hydroxyphenyl) 2,4 hexadiene

Dienestrol occurs as colorless or white needle-like crystals or as a white crystalline powder. It is readily soluble in acetone, alcohol, ether,

A solution of 0.1 Gm. of dienestrol in 10 cc. of warm normal sodium hydroxide is clear; on dilution with 20 cc. of distilled water and addition of 5 drops of 10 per cent sodium sulfide solution, the mixture does not darken more than a control solution containing 0.02 mg. of added lead.

When dried to constant weight at 100°C., an accurately weighed sample of dienestrol loses not more than 0.5 per cent in weight. It yields not more than 0.05 per cent of residue on ignition. (U. S. P. XIII, p. 695.)

Transfer to a suitable flask about 0.5 Gm. of previously dried dienestrol, accurately weighed, and add 2 cc. of acetic anhydride and 4 cc. of dry pyridine. Boil the mixture under a reflux condenser for 15 minutes, cool, add 50 to 60 cc. of distilled water and shake the flask and contents thoroughly. Stopper the flask and place it in the refrigerator over night. Collect the precipitate on a suitable tared filter and wash it with four 15 cc. portions of distilled water. Dry the precipitate at 75 to 80°C. for five hours, cool and weigh. The weight of the dry diesterol diacetate obtained, when multiplied by 0.760, corresponds to a dienestrol content of not less than 98 per cent and not more than 101 per cent. The dienestrol diacetate obtained melts at 119° to 120°C.

DIETHYLSTILBESTROL DIPROPIONATE.—The dipropionyl ester of α,α' -diethyl-4,4'-stilbenediol.— $C_{24}H_{28}O_4$ —M. W. 380.46.

Diethylstilbestrol dipropionate occurs as an odorless, tasteless, white, crystalline powder which melts at 105-107° C. It is readily soluble in acetone, benzene, ether, chloroform, hot ethyl alcohol and hot methyl alcohol, soluble in vegetable oils, very slightly soluble in water and dilute mineral acids; and insoluble in aqueous alkalis. A suspension of 0.1 Gm. of diethylstilbestrol dipropionate in 10 cc. of diluted alcohol is neutral to litmus paper.

Dissolve 10 mg. of diethylstilbestrol dipropionate in 2 cc. of concentrated sulfuric acid: an orange color is produced which disappears on dilution with water. Add 1 cc. of 50 per cent solution of antimony pentachloride in dry alcohol-free chloroform to 5 cc. of a dilute solution of diethylstilbestrol dipropionate in the same solvent a red colored solution is produced. The residue obtained in the assay for diethylstilbestrol dipropionate melts at 168-171°C and responds to tests for diethylstilbestrol.

Dry an accurately weighed specimen of diethylstilbestrol dipropionate to constant weight in a partial vacuum at 80° C., the loss in weight does not exceed 0.5 per cent. Ignite an accurately weighed specimen of diethylstilbestrol dipropionate after the addition of concentrated sulfuric acid, the residue does not exceed 0.05 per cent.

Dissolve accurately weighed specimen of diethylstilbestrol dipropionate in 2 cc. of concentrated sulfuric acid: an orange color is produced which disappears on dilution with water. Add 1 cc. of 50 per cent solution of antimony pentachloride in dry alcohol-free chloroform to 5 cc. of a dilute solution of diethylstilbestrol dipropionate in the same solvent a red colored solution is produced. The residue obtained in the assay for diethylstilbestrol dipropionate melts at 168-171°C and responds to tests for diethylstilbestrol.

equivalent to not less than 98 per cent nor more than 100.5 per cent of the weight of the specimen

DIGALEN (HOFFMANN-LA ROCHE)—The cardioactive principles of digitalis as isolated by Cloetta.

This preparation is a colorless or slightly yellowish liquid of an agreeable aromatic odor with a sweet taste which subsequently becomes bitter.

The active derivative contained in the preparation is an amorphous, white or slightly yellow powder. It dissolves readily in alcohol and chloroform, and less readily in ether. It has an intensely bitter taste and causes violent sneezing when introduced into the nose.

To 2 cc. of the preparation add a few drops of dilute acetic acid and extract with chloroform. Evaporate the chloroform extract and dissolve the residue in about 2 cc. of glacial acetic acid containing a trace of ferric chloride. To this solution add strong sulfuric acid without mixing so as to form a separate layer. A brown ring forms between the two layers which becomes broader after some hours and expands toward the top in a blue-green to black shade and toward the bottom in a reddish brown one. The acetic acid finally acquires a dark green blue color.

DIGIFOLIN (CIBA)—A digitalis preparation containing the therapeutically desirable constituents of digitalis leaf.

This preparation is almost colorless and odorless, with a slightly bitter taste. It is an amorphous brownish powder soluble in water, methyl alcohol and ethyl alcohol; insoluble in ether and petroleum ether.

Prepare two solutions. (A) Dissolve 5 Gm. ferric sulfate in 100 cc. water, filter and add 5 cc. of the filtrate to 500 cc. of pure glacial acetic acid. (B) add (cautiously) 5 cc. of the ferric sulfate solution to 500 cc. pure sulfuric acid. Dissolve a trace of the preparation in 5 cc. of solution A and layer this solution carefully on 5 cc. of solution B. At the point of contact, a dark band appears. The lower layer assumes a red color and the upper layer a bluish-green color. On standing the bluish-green layer turns to indigo-blue.

DIGILANID (SANDOZ)—A mixture of the isomorphous crystallized cardioactive glycosides lanatoside A ($C_{40}H_{72}O_{19}$), lanatoside-B ($C_{40}H_{72}O_{20}$) and lanatoside-C ($C_{40}H_{72}O_{20}$), obtained from the leaves of *Digitalis lanata*. The three components are present in the mixture in the proportions in which they occur in the crude drug, namely about 47 per cent lanatoside A, 16 per cent lanatoside-B and 37 per cent lanatoside C.

The air-dried mixture occurs as a white, odorless powder possessing a bitter taste, soluble in methanol, 1 in 20, very slightly soluble in water, 1 in 10,000 and insoluble in ether. This preparation when heated rapidly, melts with decomposition above 245°C.

Transfer 2 mg. of the glycoside mixture to a 15 cm. test tube and add 4 cc. of glacial acetic acid and one drop of ferric chloride T.S. Add from a pipet 4 cc. of sulfuric acid to underlay the acetic acid solution and allow to stand one hour. A blue color appears in the upper zone (digucose) and a violet brown in the lower zone (mixture of aglycones). Transfer about 0.02 Gm. of the glycoside mixture to a 10 cm. test tube and add 1 cc. each of water, methanol and lead acetate T.S. No immediate precipitate or coloration occurs (appreciable amounts of tannoid substances). Transfer about 20 mg. of the glycoside mixture to a test tube and add 2 cc. of methanol, 2 cc. of water and 0.5 cc. of alkaline cupric tartrate T.S. and heat for ten seconds. No turbidity appears (free reducing sugars).

Transfer about 20 mg. of the glycoside mixture, dried under vacuum and accurately weighed to a 10 cc. volumetric flask and make up to volume with ethanol. Mix, transfer to a 2 dm. polarimeter tube and observe

hydroxylamine hydrochloride in 1 cc of water. Cover with a watch glass and heat on a steam bath for one-half hour. Cool in ice water and add strong ammonia solution until the oxime precipitates. Collect the oxime on a filter, wash with 3 cc. of water containing 1 per cent ammonia (made by diluting 1 cc ammonia T S to 10 cc.), remove the excess water by suction and dry the precipitate for 4 hours at 100° C. the dihydrocodeinone oxime melts with decomposition between 264 and 268° C.

Prepare a one-tenth molar solution of dihydrocodeinone bitartrate in freshly boiled and cooled distilled water the pH of the solution is between 3 and 4. Ignite about 200 mg of dihydrocodeinone bitartrate, accurately weighed, the ash residue is not more than 0.05 per cent. Add about 100 mg of dihydrocodeinone bitartrate to 5 cc of sodium hydroxide T S, and heat the mixture to boiling; no odor of ammonia is detected.

Transfer about 150 mg of dihydrocodeinone bitartrate accurately weighed, to a 250 cc separator with the aid of 10 cc. of water. Drop a small piece of red litmus paper into the funnel and then add dropwise, ammonia T S until the litmus paper just turns blue (about 3 drops). Extract six times with 2¹/₂, 25, 20, 20, 15 and 15 cc. portions of chloroform, and collect the chloroform extracts in a 250 cc. Erlenmeyer flask after filtering through a small plug of cotton. Evaporate the combined chloroform extracts almost to dryness, remove the flask from the steam bath blowing off the remainder of the chloroform with a stream of air. Add 5 cc of neutral alcohol and heat on a steam bath until the residue dissolves. Add 2 drops of methyl red indicator T S and then 20 cc of 0.02 N sulfuric acid. Heat on a steam bath until the alcohol starts to reflux. Cool the flask to room temperature and titrate the excess acid with 0.02 N sodium hydroxide. Each cc of 0.02 N sulfuric acid consumed is equivalent to 0.009434 Gm of dihydrocodeinone bitartrate. The amount of dihydrocodeinone bitartrate found is not less than 98 per cent of the sample as received.

DIHYDROXY ALUMINUM AMINOACETATE.—

$\text{Al}(\text{C}_2\text{H}_5\text{NO}_2)_3 \cdot 3\text{H}_2\text{O}$ —M W 135.05.—Basic aluminum aminoacetate.—

A basic aluminum salt of glycine containing small amounts of aluminum hydroxide and glycine.

Dihydroxy aluminum aminoacetate is a white colorless powder with a faint sweet taste. It is insoluble in water and organic solvents but soluble in dilute mineral acids and solutions of fixed alkalis to yield a cloudy solution which clarifies on heating.

Dry 2 Gm of dihydroxy aluminum aminoacetate accurately weighed, to constant weight at 150° C. This requires drying for two to three days. The loss in weight does not exceed 16.5 per cent.

Prepare a suspension of 1 Gm of finely ground dihydroxy aluminum aminoacetate in a glass stoppered flask containing 25 cc. of distilled water. Mix the contents for 5 minutes.

The ...

... aminoacetate,
5 cc. of tenth,
for 5 minutes,
30

... dihydroxy aluminum
... and dropwise until the compound just
dissolves to form a clear solution. Divide the solution into two equal
portions. To one portion add an excess of diluted ammonia solution; a
white flocculent precipitate of aluminum hydroxide is formed which is
insoluble in an excess of ammonia but soluble in sodium hydroxide T S.
To the other portion add one drop of 1 per cent phenol and 5 cc of 0.02 N
sulfuric acid. A blue color is produced characteristic of glycine.

... aminoacetate shows no heavy metals when sub-
jected to the test outlined in the 1.5 P. III p. 61. Dihydroxy alu-
minum aminoacetate should be free of nitrogen when ...

1 cc. of the sample
shaken with 10 cc. ...
precipitation 2 mg. per
average through F ...
3 January 1946, p. 41

Supernatant 5 Gm. of dihydroxy aluminum aminoacetate in 100 cc.

p. 20.

precipitate with hot water
the precipitate, ignite it at
weigh the aluminum oxide
content of dry dihydroxy
nor more than 38.7 per cent.

Determine the nitrogen content by the semimicro Kjeldahl
U. S. P. XIII, p. 673, using 0.1 Gm. of dried dihydroxy alumi
acetate, accurately weighed. The per cent of nitrogen pres
dihydroxy aluminum aminoacetate is not less than 9.8 nor more
per cent

DIIDO-HYDROXYQUINOLINE. — $C_{10}H_8I_2$
M. W. 397.34.—5,7-Diiodo-8-hydroxyquinoline.

sition

Warm a few crystals of diodo-hydroxyquinoline with 1 cc.
trated sulfuric acid vapors of iodine are evolved. Heat 0
diodo-hydroxyquinoline mixed with 5 Gm. of anhydrous sodium
in a deep crucible, cool, extract the mixture in 10 cc.
acidify with diluted nitric acid. Filter and add 13 cc. of ten
silver nitrate to the filtrate. Shake to coagulate the
and filter. Add 1 cc. of tenth normal silver nitrate to the
shake and filter through a fresh filter paper. Wash
precipitate on the filter a yellow color is observed (distinction
Vioform, which gives a white precipitate).

Dry 1 Gm. of diodo-hydroxyquinoline over phosphorous pent
24 hours the loss in weight is less than 0.1 per cent.

Incinerate about 1 Gm. of diodo-hydroxyquinoline: the ash is
0.5 per cent

Mix about 0.15 Gm. of diodo-hydroxyquinoline, accurately
in a nickel crucible with 5 Gm. of anhydrous potassium
Mix thoroughly with a dry stirring rod, settle the mixture
tapping the crucible, overlay with 5 Gm. of potassium
(or sodium carbonate) and ignite at about 600°C. for 1
to eight minutes. Cool, transfer the crucible to a 500
mouth conical flask and extract with about 20 cc. of distilled
Acidify the solution carefully, dropwise, with five normal hydro
acid

glass

flask

Add

titled

to 0.005076 Gm. of iodine. Diodo-hydroxyquinoline contains not less than 60.5 per cent nor more than 64.0 per cent of iodine.

2,3-DIMERCAPTOPROPANOL IN OIL.— $C_3H_8OS_2$ —M. W. 124.21—A solution of 2,3-dimercaptopropanol 10 per cent in peanut oil, containing benzyl benzoate 20 per cent.

2,3-Dimercaptopropanol in oil is a yellow viscous solution possessing a pungent offensive odor. The benzyl benzoate and peanut oil used in the preparation of the solution meet with the requirements of the U. S. Pharmacopeia.

Dilute approximately 1 Gm. of 2,3-dimercaptopropanol in oil, accurately weighed by difference, with 15 cc. of chloroform and 40 cc. of methyl alcohol. Titrate the resulting solution with tenth normal iodine solution to a permanent yellow color, or if desired, add an excess of the iodine solution and back titrate with tenth normal sodium thiosulfate solution. Each cc. of tenth normal iodine solution is equivalent to 0.00621 Gm. of 2,3-dimercaptopropanol.

DIPERODON.—The di phenylurethane of 1 piperidinopropane-2,3-diol—Piperidinopropanediol di phenylurethane— $C_{22}H_{27}N_3O_4$ —M. W. 397.46—Prepared by combining piperidine and glycerol monochlorohydrin in the presence of alkali and reacting the piperidinopropanediol with phenyl isocyanate.

Diperodon occurs as a fine white odorless, crystalline powder, which is nonvolatile and stable in air at ordinary room temperatures. The powder is tasteless but produces a slight sense of numbness. It is insoluble in cold water, slightly soluble in petroleum ether and very soluble in acetone, alcohol, benzene, chloroform, ether and in ethyl acetate. It melts between 78 and 82 C. and is very slowly decomposed by heating at 100 C. in air or in contact with water.

Dissolve about 0.9 Gm. of diperodon in 2 cc. of alcohol, add 2 cc. of diluted hydrochloric acid and dilute to 100 cc. with water. Mix the solution and test separate portions as follows. Add a few drops of potassium mercuric iodide T. S. to a 5 cc. portion of the solution; a yellowish white precipitate forms. Add a few drops of gold chloride T. S. to a 5 cc. portion of the solution; a yellowish orange precipitate forms (distinction from butocaine and procaine which yield brown precipitates and from cocaine, dibucaine and metylocaine which yield lemon yellow precipitates). Phenocaine yields a precipitate somewhat similar to that given by diperodon. Add a few drops of potassium permanganate T. S. to a 5 cc. portion of the solution; a lasting precipitate which turns from pink to brown within 1 minute forms (distinction from butocaine, cocaine, dibucaine, phenocaine and procaine which do not immediately yield lasting precipitates). To a 5 cc. portion of the solution add a few drops of diluted hydrochloric acid and a few drops of 10 per cent sodium nitrate solution followed by 3 cc. of a 2 per cent solution of β -naphthol in 10 per cent sodium hydroxide solution; a white precipitate changing to yellowish white and finally to light orange forms (distinction from butocaine and procaine which yield red brown precipitates).

Saturate 25 cc. of the solution with hydrogen sulfide; no precipitate or color develops.

Dissolve about 0.1 Gm. of diperodon in 1 cc. of sulfuric acid; the solution is colorless (readily carbonizable substances).

Ignite about 0.5 Gm. of diperodon accurately weighed; the residue is not more than 0.2 per cent.

Dry about 0.5 Gm. of diperodon accurately weighed in a desiccator over phosphorus pentoxide; the loss in weight does not exceed 4 per cent.

Weigh accurately about 0.3 Gm. of diperodon and dissolve the sample in 10 cc. of ethyl alcohol previously neutralized to methyl red T. S. Add exactly 10 cc. of 0.1 N hydrochloric acid and 40 cc. of water. Warm gently if necessary, to obtain a clear solution. Cool to room temperature, add 3 drops of methyl red T. S. and titrate to the bronze color of the indicator with 0.02 N sodium hydroxide. Each cc. of 0.1 N hydrochloric acid is equivalent to 0.3974 Gm. of anhydrous diperodon; the amount

of anhydrous dipiperodon found corresponds to not less than 94.0 nor more than 95.5 per cent of the sample weight

DIPERODON HYDROCHLORIDE.— $C_{22}H_{27}N_3O_4HCl$.—M. W. 433.92.—*di*-Phenylurethane of 1-piperidinopropane-2,3-diol hydrochloride.

Diperodon hydrochloride occurs as a fine, white crystalline, odorless powder; when applied to the tongue, it produces a bitter taste followed by a sense of numbness. It is stable in air at ordinary temperatures. Diperodon hydrochloride is slightly soluble in water, acetone and ethyl acetate; soluble in alcohol; insoluble in benzene and ether. Its aqueous solution (1 in 100) is faintly acid to litmus. Diperodon hydrochloride melts at 195° to 200°C., with decomposition. From aqueous solutions, alkali carbonates and hydroxides precipitate the free base as a colorless oil, which does not solidify under ordinary conditions.

the solution of water with
0.1 Gm. of heavy metals).
hydrogen accurately weighed,
Dry about 0.5 per
at 100°C. cent
cent Inci
weighed: the residue is not more than 0.1 per cent. Transfer about 0.3 Gm of dipiperodon hydrochloride, accurately weighed, to a 500 cc Kjeldahl flask, and determine the nitrogen content according to the official method described in *Methods of Analysis of the Association of Official Agricultural Chemists*, 6 ed., page 26, paragraph 25. the percentage of nitrogen corresponds to not less than 9.5 per cent, nor more than 9.8 per cent when calculated to the dried substance. Dissolve about 0.25 Gm of dipiperodon hydrochloride, accurately weighed, in 25 cc. of water, by warming, and transfer to a 500 cc. Squibb separatory funnel, rinse twice using about 10 cc of water, followed by the addition of 3 cc. of a dilute ammonium hydroxide (one part of diluted ammonia solution and ten parts of water), extract with four successive portions of ether using 20 cc each, filter through a pledget of cotton and evaporate to a thick oil in a stream of warm air; dissolve the oily residue in about 25 cc of previously neutralized alcohol; warm slightly, add 10 cc of tenth normal hydrochloric acid solution, followed by the addition of 10 cc. of water; determine the excess of acid by titration with tenth normal sodium hydroxide solution using bromphenol blue T.S. as an indicator. The residue should not

hydrogen content to not less than 8.35 per cent, nor more than 8.45 per cent calculated to the dried substance.

of tenth-normal sulfuric acid, shake vigorously, and separate. Add 5 cc. more of the tenth-normal sulfuric acid and repeat the shaking. Combine the two acid extractions. Rinse the ether with two 5 cc. portions of water and combine with the acid solution. Add sodium hydroxide to a methyl red end point. The sodium hydroxide is equivalent to 0.02918 the diphenhydramine hydrochloride nor more than 105 per cent.

DYMIKAL (MCNEIL LABS.).—A mixture of three dyes containing crystal violet 46 per cent, brilliant green 31 per cent and acriflavine 23 per cent. It may be prepared by mechanical mixing of the three dyes in their solid state.

This dye mixture is soluble in water, forming a neutral greenish blue solution which shows a yellow fluorescence under ultraviolet light.

The crystal violet used in the mixture meets the standards set forth for methylosaniline chloride in the U. S. P. XIII, p. 326. The brilliant green used complies with the standards for brilliant green N. N. R. The acriflavine used meets the standards set forth for acriflavine in N. F. VIII, p. 25.

Prepare an adsorption column by tamping dry Celite No. 545 (Johns Manville) into a glass tube approximately 8 mm. by 350 mm. Pour 5 cc. of an aqueous solution containing approximately 0.5 mg. of the dye mixture onto the dry column and allow it to filter down the column aided by suction. Just before the last bit of liquid disappears from the top of the column add an aqueous solution of acetone (22% V/V) to

to a concentration of 1% acriflavine. Measure using a solution viscometer, as a not less than

Determine the quantities of crystal violet and brilliant green in the mixture by measuring the light absorption (E instrumental) of appropriate dilutions in 50% V/V aqueous alcohol at wavelengths of 5800, 5900, 6000, 6100, 6200 and 6300 Å in a spectrophotometer. For comparison, determine the $E_{\frac{1\%}{1\text{ cm}}}$ values for crystal violet alone and for brilliant green alone, using concentrations similar to those expected in the unknown solution. To calculate the $E_{\frac{1\%}{1\text{ cm}}}$ values, divide the E instrumental values by the product of the cell thickness and the concentration used in grams per 100 cc. Calculate the percentage of brilliant green and crystal violet present in the diluted solution from a set of equations valid at each wavelength as follows:

$$E_{\text{observed}} \text{ for the dye mixture} = (X \text{ times } E_{\frac{1\%}{1\text{ cm}}} \text{ for crystal violet}) + (Y \text{ times } E_{\frac{1\%}{1\text{ cm}}} \text{ for brilliant green})$$

$100 \frac{X}{c}$ equals the percentage of crystal violet and $100 \frac{Y}{c}$ represents the percentage of brilliant green, where c equals concentration in grams per 100 cc. of the dye mixture measured by this method, the preparation contains not less than 42 per cent nor more than 48 per cent of crystal violet and not less than 27 per cent nor more than 35 per cent of brilliant green.

EPINEPHRINE IN OIL SUSPENSION, 1:500.—A 0.2 per cent suspension, containing 1 part of epinephrine U. S. P. to 500 parts of vegetable oil.

Epinephrine in oil occurs as a pale yellow to white milky suspension

from which a white solid settles out on standing. Centrifuge an ampul of epinephrine in oil until the crystals have collected in the bottom, open the ampul, decant the clear oil, and wash the residue with two 1 cc. portions of acetone by decantation. The residue, dried at 75°C., melts above 215°C., when heated at a rate of 8 degrees per minute.

Transfer an accurately measured volume of epinephrine in oil, containing approximately 8 mg. of epinephrine to a centrifuge tube. Centrifuge, wash and dry as described above. Dissolve the residue in 0.40 cc. of normal hydrochloric acid filter and polarize in a micro-polariscope tube. The specific rotation $[\alpha]_{\frac{25}{D}}$ is between -50.0 and -53.5 degrees.

Shake 10 cc. of epinephrine in oil with 50 cc. of tenth normal hydrochloric acid add 20.0 cc. of distilled water, shake, filter through a paper previously moistened with water. Discard the first 5 cc. and save the remainder for the test. To 20.0 cc. of 0.5 per cent potassium

per cc

ESTRIOL.— $C_{18}H_{26}O_3$ —M. W. 288.37—3,16,17-trihydroxy- Δ -1,3,5-estratriene. A crystalline estrogenic steroid isolated from the urine of pregnant women.

Estrisol occurs as a white, odorless, microcrystalline powder, practically insoluble in water but soluble in alcohol, dioxane and oils. During heating on a hot stage of a microscope, a phase change occurs between 270° and 275° C. and the material melts sharply at 282° C. (rate of heating, 4° a minute—Kofler microscope heating stage). On heating for five hours in an Abderhalden drier at 80° C. under a vacuum of 2 mm., 20 mg. estrisol loses no appreciable weight.

Transfer approximately 40 mg. of estrisol, accurately weighed, to a 1 cc. microvolumetric flask, fill to the mark with freshly distilled dioxane and determine the optical rotation after the U. S. P. method, using a 2 dm. microtube. The specific rotation $[\alpha]_{\frac{25}{D}}$ is + 58 degrees (\pm 5 degrees).

Dissolve approximately 60 mg. of estrisol accurately weighed, in a mixture of pyridine (6 cc.) and acetic anhydride (2 cc.) and heat under a micro reflux condenser for twenty-four hours at 95°C. Transfer the solution to a 250 cc. flask containing 100 cc. of ice-cold water and titrate with tenth normal sodium hydroxide. The acetic acid value is not more than 1.4 nor less than 321 equivalent to three acetylated hydroxyl groups. [A blank determination must be made for pyridine acetic acid and anhydride] (*J. Biol. Chem.* 91: 655, 1931).

Dissolve approximately 40 mg. of estrisol in a mixture of pyridine (6 cc.) and acetic anhydride (2 cc.) and heat under a micro reflux condenser for 21 hours at 95°C. Let stand at 37°C. for another 24 hours. Add 10 cc. of 50 per cent alcohol and evaporate under vacuum to a thick syrup. Add very gradually about 1 cc. of alcohol and set aside for crystallization. Filter the crystals and redissolve in 3 cc. of 95 per cent alcohol. Evaporate the alcohol and dissolve the residue in 4 cc. of pyridine. After addition of 16 cc. of water a white flocculent precipitate occurs. Recrystallize twice from 90 per cent alcohol, dry the crystals in vacuum at 80°C. over phosphorus pentoxide. The melting point of the triacetate is 126°C. (\pm 1 degree).

Add about 2 mg. of estrisol, accurately weighed, in a tared platinum micro boat. No residue should remain. Micro carbon and hydrogen analysis,

pentoxide in a vacuum is not more than 3 per cent. The residue on
 in form in 100 cc of a 1
 normal hydrochloric acid at
 of the National Institute
 Service

FOLIC ACID—Pteroylglutamic acid—N-4- { (2-amino-4
 hydroxy-6-pteridyl)methyl}amino } benzoyl}glutamic acid —
 $C_{19}H_{19}O_6N_7$ —M W 441.4

Folic acid occurs as a yellowish-orange crystalline powder. It is
 soluble in alcohol, benzene, chloroform, ether and water, very slightly
 soluble in hot water, and sparingly soluble in tenth normal sodium
 hydroxide.

Place about 0.1 Gm. of folic acid, accurately weighed, in a dry 125 cc.,
 as methanol
 ury by the
 Am. Chem.
 her reagent
 Alternatively,
 vacuum over
 120 hours
 cent
 ighed Cool,
 Cautiously
 0.5 per cent

on the dry basis.

Treat the residue from the sulfated ash with 23 drops of hydrochloric
 acid and evaporate to dryness on a steam bath. Add 10 cc. of 2 per cent
 hydrochloric acid and heat for 5 minutes on a steam bath. Filter through
 paper into a Nessler tube. Repeat the acid treatment of the residue with
 10 cc. more of 2 per cent hydrochloric acid. Dilute the combined filtrates
 to 25 cc., and add 10 cc. of hydrogen sulfide T.S. Keep in the dark for
 10 minutes. No more turbidity develops than corresponds to 50 ppm. of
 lead (U. S. P. XIII).

Place about 0.1 Gm. of *para*-aminobenzoic acid, of known purity, ac-
 curately weighed, in a 100 cc. volumetric flask. Add 50 per cent alcohol
 to dissolve the solid, and dilute to the mark with 50 per cent alcohol.

concentration of total amine in the solution in terms of *p*-aminobenzoic acid.

Calculate the folic acid present from the following equation:

$$\frac{(\text{micrograms total amine as } p\text{-aminobenzoic acid} - \text{micrograms free amine as } p\text{-aminobenzoic acid}) \times 3.22}{\text{folic acid found.}}$$

The folic acid content is not less than 90 per cent calculated on the dry basis.

FOLIC ACID TABLETS. Weigh, accurately, 25 tablets of folic acid and grind them to a fine powder in a mortar. Weigh out an amount of powder equivalent to 0.1 Gm. of folic acid. Transfer the weighed portion to a 100 cc. volumetric flask and dilute to 100 cc. with tenth-normal sodium hydroxide. Centrifuge and transfer 1 cc. of the supernatant liquid to a 100 cc. volumetric flask. Continue the assay for folic acid as directed in the monograph for folic acid, beginning with the sentence, "Transfer 1 cc. of the solution to a 100 cc. volumetric flask and add 80 cc. of water, 10 cc. of five normal hydrochloric acid . . ." The folic acid content of the tablets is not less than 90 nor more than 115 per cent.

GASTRIC MUCIN. *Monograph published by American Pharmacopoeia Commission.*

cent.

Incinerate approximately 1 Gm. of gastric mucin, accurately weighed, in a muffle furnace at 500 C.: the ash content does not exceed 65 per cent.

Transfer a 10 Gm. sample of gastric mucin to a 125 cc. Erlenmeyer flask and add 100 cc. of 70 per cent alcohol (737 cc. of U. S. P. alcohol diluted to 1 liter). Stopper the flask, shake the mixture for thirty minutes and decant the supernatant liquid. Repeat this addition of alcohol and extraction for a total of six times. Measure the combined extracts and filter a portion through a dry filter paper. Evaporate 50 cc. of the filtrate to dryness, dry at 100 C. and 72 cm. of mercury to constant weight, and calculate the dry weight, *S*, in the total volume of alcohol. The mucin content, calculated as $(10 - S) \times 10$, is not less than 73 per cent nor more than 90 per cent.

Determine the nitroge
(described in the foreg
ing to *Methods of Ana*
Chemists, 6, ed., p. 25.
than 9.0 per cent.

Transfer 0.1 Gm. of the dried alcohol insoluble residue as previously obtained to a 125 cc. Erlenmeyer flask and add 50 cc. of two-normal sulfuric acid. Digest on a steam bath under a reflux condenser for three hours and dilute to 100 cc. Transfer 4 cc. of this solution to a 25 by 200 mm. test tube, add 1 drop of phenolphthalein and neutralize with 30 per cent sodium hydroxide. Add 5 cc. of standard copper reagent [Twenty-five Gm. of anhydrous sodium carbonate, 20 Gm. of sodium bicarbonate and 25 Gm. of potassium sodium tartrate are dissolved in 600 cc. of distilled water; 7.5 Gm. of $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ is dissolved in 100 cc. of water and introduced with constant stirring into the carbonate tartrate solution through a funnel resting on the bottom of the container. To the solution add 5 Gm. of potassium iodide and 22 cc. of an alkaline standard normal solution of potassium bionate (32.498 Gm. of potassium bionate and 83.3 cc. of normal sodium hydroxide made up to 1 liter). The resultant solution is made up to exactly 1,000 cc.] and make up to 10 cc. Cover the test tube with a small beaker and suspend it in boiling water for fifteen minutes and then cool in a pan of cold water without shaking. Add 5 cc. of normal sulfuric acid and after one minute titrate with 0.005 normal sodium thiosulfate, using

starch as an indicator. The sodium thiosulfate is standardized against the 0.022 normal copper sulfate iodate reagent, 5 cc of which should require 22.0 cc. of the thiosulfate. The difference between this control figure and the number of cubic centimeters of thiosulfate used in the determination should not be less than 8.6 nor more than 12.2 cc.; that is, not less than 25 per cent nor more than 35 per cent of reducing material, calculated as dextrose in the alcohol insoluble material.

Prepare a 2 per cent solution of gastric mucin by triturating 2 Gm of mucin with 100 cc. of water and passing it through a 60 mesh screen. Determine the pH of this solution by means of a glass electrode at 25 C.; the pH is not below 3.7 nor above 6.5. Determine the viscosity of this solution at 25 C. within one hour by means of a 10 cc. Mohr pipet and compare it with water; the relative viscosity is not below 1.30 nor above 3.50.

GITALIN (AMORPHOUS).—A glycosidal constituent of *Digitalis purpurea* Linné prepared according to the method of Krait.

Gitalin (amorphous) is a white or slightly buff colored amorphous powder, insoluble in water and alcohol, is neutral, sharp melt 110 C and its aqueous hydrogitalin, 1 per cent acetic acid cent ferric test sulfuric. The upper changing to white chloride, 1 per cent acetic acid 10 mg of ex a brown an aqueous 100°C, its water-drop is to the color of digitoxin.

GOLD SODIUM THIOMALATE— $C_4H_3AuNa_2O_4S$
 H_2O —M W 408.33—Disodium aurothiomalate

Gold sodium thiomalate occurs as a fine, white to yellowish white powder possessing a metallic taste. It is very soluble in water and practically insoluble in alcohol and in ether. Aqueous solutions of gold sodium thiomalate are stable in the dark at room temperature.

Weigh accurately about 0.5 Gm. of gold sodium thiomalate and transfer it to a 300 cc. Kjeldahl flask with about 10 cc. of water, add 20 cc. of nitric acid and mix well. Add 15 cc. of sulfuric acid slowly with mixing and heat over a low flame, at first gently boiling and later increasing the heat until fumes of sulfur trioxide are evolved. Allow the flask and contents to cool to room temperature and add 30 cc of water slowly with mixing. The precipitated gold should agglomerate and the liquid should not have a purplish color (*colloidal gold*). If the liquid is not colorless, add 20 cc. of 3 per cent hydrogen peroxide, reheat as directed, recool and redilute. Filter through an ignited tared Gooch crucible, wash with water, dry at 100° C., ignite, cool and weigh: the weight of gold found corresponds to not less than 49.5 per cent nor more than 50.7 per cent, calculated to the dried substance.

HEPARIN SODIUM.—The hydrated sodium salt of a naturally occurring, complex organic polymer possessing anticoagulant properties. The chemical structure of heparin has not been fully established. It is considered to be a dextrorotatory polysaccharide made up of hexosamine and hexuronic acid units containing sulfuric acid ester groups.

Heparin sodium occurs as a white to lightly colored, amorphous, gumlike powder. It is very soluble in water but practically insoluble in alcohol, ether, and acetone. The pH of a 1 per cent solution (made by dissolving 1 cc. of water containing 1 cc. of heparin sodium) is 4.5. The color of the mixture of petroleum ether and heparin sodium is pale blue.

shake the mixture vigorously for one minute. Allow the emulsion to break: the color of the solution returns to pale blue and a purple precipitate collects in the interface between the liquids.

Place 1 cc. of 1 per cent heparin sodium in a test tube, add 2.5 cc. of ortho-phenanthroline T.S.: a red precipitate forms.

Fuse about 50 mg. of heparin sodium with a small piece (2 mm) of metallic sodium in a test tube; cool, add 5 drops of alcohol, leach the fused mass with 5 cc of water and filter: the filtrate responds to tests for cyanide and sulfide, indicating the presence of nitrogen and sulfur respectively.

Add 1 drop of strong ammonia solution and 3 drops of 30 per cent hydrogen peroxide solution to 0.5 cc. of 1 per cent heparin sodium solution contained in a test tube. Heat on a water (steam) bath for ten minutes: no cloudiness results which cannot be cleared by making the solution acid to congo red, by the addition of just sufficient diluted hydrochloric acid (*barium ion*).

Mix 5 cc. of 1 per cent heparin sodium solution with 5 cc. of sulfosalicylic acid reagent (dissolve 20 Gm of sodium sulfate decahydrate in 80 cc of water, cool to 35° C., add 5.0 Gm of sulfosalicylic acid, dissolve and dilute to 100 cc.). Heat the mixture to boiling: no cloudiness should be discernible (*protein*).

Ash 0.1 Gm of heparin sodium in the presence of sulfuric acid in a tared porcelain crucible: the sulfated ash amounts to not more than 40.5 per cent of the dried substance.

Dry about 0.1 Gm. of heparin sodium for twenty-four hours at room temperature over phosphorus pentoxide in a vacuum desiccator at a pressure not above 5 mm. of mercury: the loss in weight is not more than 12 per cent.

Heparin sodium shall meet the pyrogen test described in the U. S. P. XIII when solutions containing 1,000 units per cubic centimeter are injected in a dosage of 20 cc per kilogram of body weight.

HEXESTROL.— $C_{18}H_{22}O_2$.—M W. 270.36.—*Meso*-3,4-di-*para*-hydroxyphenyl-*n*-hexane

Hexestrol occurs as an odorless white crystalline powder which melts

at 185-188° C. It is freely soluble in ether; soluble in acetone, alcohol and methanol, slightly soluble in benzene and chloroform, and practically insoluble in water and in dilute mineral acids. It may be dissolved in vegetable oils and in dilute solutions of sodium or potassium hydroxide. When recrystallized from diluted alcohol, hexestrol appears in the form of thin platelike crystals of irregular, serrated outline.

Dissolve about 10 mg of hexestrol in 10 cc of diluted alcohol and add three drops of 1 per cent ferric chloride T.S. a yellowish green color develops which changes to yellow. Add a few drops of 50 per cent solution of antimony pentachloride in dry alcohol free chloroform to a very dilute solution of hexestrol in the same solvent a red colored solution is produced. Dissolve 10 mg of hexestrol in 5 cc of concentrated sulfuric acid no color is produced (distinction from diethylstilbestrol which yields an orange color).

The hexestrol diacetate obtained in the assay given below melts at 137-139° C.

Dry an accurately weighed specimen of hexestrol to constant weight at 100° C. the loss does not exceed 0.5 per cent. Ignite an accurately weighed specimen of hexestrol the residue is not more than 0.05 per cent. Dissolve 0.1 Gm of hexestrol in 10 cc of warm sodium hydroxide T.S. the solution is clear and colorless, dilute to 20 cc with distilled water and add 5 drops of 10 per cent sodium sulfide solution the darkening produced does not exceed that of a control to which has been added 0.02 mg of lead.

Transfer to a suitable flask about 0.5 Gm of dried hexestrol, accurately weighed and add 2 cc of acetic anhydride and 4 cc of dry pyridine. Boil the mixture under a reflux condenser for fifteen minutes, cool, add 50-60 cc of distilled water and shake the flask and contents thoroughly. Stopper the flask and place it in the cold for one to one and one half hours. Collect the precipitate on a suitable filter and wash it with four 20 cc portions of distilled water. Dry the precipitate at 75-80° C overnight, cool and weigh the weight of the dry hexestrol diacetate obtained, when multiplied by 0.7628 corresponds to a hexestrol content of not less than 98.5 per cent and not more than 100.5 per cent.

HEXETHAL SODIUM — $C_{12}H_{19}N_2NaO_4$ — M W 262.29 — The monosodium salt of 5 α hexyl 5 ethylbarbituric acid

Caution. Aqueous solutions of hexethal sodium are not stable but decompose on standing, on boiling precipitation occurs with evolution of ammonia.

Hexethal sodium is an odorless, white or slightly yellowish powder, with a bitter taste. It is very soluble in water, soluble in alcohol and practically insoluble in ether and benzene. An aqueous solution of hexethal sodium has an alkaline reaction to litmus.

Dissolve about 0.5 Gm of hexethal sodium in 100 cc of water, add an excess of diluted hydrochloric acid, collect the resultant hexylethyl barbituric acid on a filter, wash and dry at 90° C. it melts at 122-125° C. Incinerate about 1 Gm of hexethal sodium, the residue responds to tests for sodium carbonate. Boil about 0.5 Gm of hexethal sodium with 5 cc of a 25 per cent sodium hydroxide solution, it is decomposed with evolution of ammonia. Dissolve about 0.3 Gm of hexethal sodium in 10 cc of water and divide into two portions, to one portion add 1 cc of mercuric bichloride T.S. a white precipitate results, soluble in an excess of strong ammonia solution. To the other portion add 5 cc of silver nitrate T.S. a white precipitate results, soluble in an excess of strong ammonia solution.

Dissolve about 0.3 Gm of hexethal sodium in 50 cc of water, add 5 cc of diluted nitric acid and filter through paper. separate portions of 10 cc each of the filtrate yield no greater opalescence on the addition of 1 cc of silver nitrate T.S. than that produced by 0.25 cc of tenth normal hydrochloric acid in 50 cc of water (chloride), no turbidity on the addition of 1 cc of barium nitrate T.S. (sulfate). To about 0.3 Gm of hexethal sodium in 25 cc of water add 1 cc of diluted hydrochloric acid, filter through paper, the filtrate yields no color or precipitate on saturation with hydrogen sulfide (salts of heavy metals). Add about

0.1 Gm. of hexethal sodium to 1 cc. of sulfuric acid; the solution is colorless (*readily carbonizable substance*).

Transfer about 0.5 Gm. of hexethal sodium to a stoppered cylinder, add 10 cc. of water, shake for ten minutes; repeat twice, utilizing the same tared beaker. The loss does not exceed 0.5 per cent.

Dry about 1 Gm. of hexethal sodium, accurately weighed, to constant weight at 100° C.; the loss does not exceed 2.5 per cent. Transfer about 0.5 Gm. of hexethal sodium, accurately weighed, to a suitable Squibb separatory funnel, add 50 cc. of water, followed by 10 cc. of diluted hydrochloric acid; extract with eight successive portions of ether of 25 cc. each, evaporate the combined ethereal extracts to dryness in a stream of warm air and dry to constant weight at 90° C.; the amount of hexylethyl barbituric acid corresponds to not less than 90.8 per cent nor more than 91.6 per cent calculated to the dried substance. Transfer the acidified aqueous portion from the foregoing extraction to a tared platinum dish

dried substance.

HEXOBARBITAL SOLUBLE. — $C_{12}H_{13}N_2NaO_3$. — M. W. 258.25.—The monosodium salt of 1,5-dimethyl-5- Δ^1 -cyclohexenyl barbituric acid.

Hexobarbital soluble occurs as a white, crystalline, odorless, hygroscopic powder, with a slightly bitter taste. It is very soluble in water, freely soluble in alcohol, and practically insoluble in ether. An aqueous solution of hexobarbital soluble is alkaline to litmus. The pH of a 10 per cent solution of hexobarbital soluble lies between 11 and 12.

Dissolve about 0.5 Gm of hexobarbital soluble in 100 cc. of water, add an excess of diluted hydrochloric acid, mix, allow to stand fifteen minutes and collect the resultant 1,5-dimethyl-5- Δ^1 -cyclohexenyl barbituric acid on a filter, wash with water and

Transfer about 0.1 Gm. of the acid to a stoppered cylinder, add for one minute, filter through paper, portion add 1 cc. of 36 per cent T.S.; an immediate discoloration of potassium permanganate T.S.

Transfer about 0.5 Gm of hexobarbital soluble to a 50 cc Erlenmeyer flask, add 5 cc. of water and about 0.4 Gm of *p*-nitrobenzyl chloride dissolved in 10 cc of 90 per cent alcohol. Attach the flask to a reflux condenser and heat the mixture on a water bath for one half hour. Cool the flask and collect the precipitate on a filter, wash with water, dry at 65° C., dissolve the dry product in just sufficient hot 60 per cent alcohol, cool and collect the precipitate, dry at 65° C.; the melting point of the product is 113-115° C.

Transfer about 0.3 Gm of hexobarbital soluble to a test tube containing 2 cc of water and add, dropwise, bromine T.S until the color of bromine faintly persists after vigorously shaking the test tube. Pour the contents of the test tube into 100 cc. of water, filter through paper, wash with water and dry at 65° C.; the melting point of the product lies between 130° and 132° C., with decomposition.

Incinerate about 1 Gm of hexobarbital soluble in a porcelain dish, cool, dissolve the residue in 50 cc of water and divide into two portions: the first portion responds to tests for sodium carbonate. Rinse the porcelain dish with 2 cc. of diluted hydrochloric acid, add the rinsings to the second portion and filter through paper; the filtrate

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T.S. (sulfate)

Add about 0.1 Gm. of hexobarbital soluble to 2 cc. of sulfuric acid.

cool in ice with an occasional swirling for twenty minutes. Then add 10 cc. of 10 per cent potassium iodide solution (iodate free) and allow to stand for ten minutes. Titrate the free iodine with tenth normal sodium thiosulfate solution. When the titration is nearly complete, add 5 cc. of chloroform, using starch T.S. as the indicator, and continue the titration until colorless. Each cc. of tenth normal bromide-bromate solution is equivalent to 0.0129 Gm. of hexobarbital soluble; the amount found corresponds to not less than 99 per cent nor more than 101 per cent.

5 cc. diluted hydrochloric acid, filter; separate portions of 10 cc. each of the filtrate yield no turbidity on the addition of 1 cc. of barium chloride T.S. (sulfate); no color or precipitate on saturation with hydrogen sulfide (salts of heavy metals).

Dry about 1 Gm. of sodium o-iodohippurate, accurately weighed, to constant weight at 100° C.: the loss in weight is not more than 10 per cent nor less than 6 per cent. Boil about 1 Gm. of sodium o-iodohippurate, accurately weighed, with 10 cc. of benzene for fifteen minutes, replacing the evaporated liquid if necessary, decant the supernatant liquid through filter paper and wash the filter with 10 cc. and 5 cc. portions, of benzene; evaporate the combined filtrates to dryness in a tared beaker and dry to constant weight at 100° C.: the residue does not exceed 0.2 per cent (uncombined o-iodohippuric acid). Transfer about 0.5 Gm. of sodium o-iodohippurate, accurately weighed, to a tared beaker, add 10 cc. of benzene, the nitrogen content accor

Methods of Analysis of the

ed. 6, p. 27, paragraph 25:

less than 4.1 per cent, nor more than 4.4 per cent when calculated to the dried substance. Weigh accurately about 1 Gm. of sodium o-iodohippurate

acid, heat cautiously while repeat twice, using por-

0.5 Gm. of ammonium

weigh as sodium sulfate:

68 per cent nor more

led substance. Transfer

sulfur bomb; determine

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ponds to not less than

calculated to the dried

substance.

HOMATROPINE HYDROCHLORIDE.— $C_{16}H_{21}NO_3$.

HCl.—M. W. 311.80.—The hydrochloride of the alkaloid

homatropine, obtained by the condensation of tropine and

mandelic acid.

Homatropine hydrochloride occurs as small white crystals, soluble

in water and alcohol and melting at from 216 to 217° C.

The color test for the identification of homatropine hydrochloride

and the tests showing the absence of impurities should agree with

those described in the U. S. Pharmacopeia under homatropine hydro-

bromide.

INVERT SUGAR SOLUTION.—A solution of a mixture

of dextrose and levulose obtained by the inversion of sucrose.

Invert sugar solution is prepared by inverting cane sugar with

tartaric acid and adjusting to a pH of 6.8 with sodium hydroxide

Invert sugar solution is a clear, pale amber, sweet, watery solution,

A 10 cc. portion requires less than 2 cc. of tenth-normal sodium

hydroxide to neutralize the acid, phenolphthalein T.S. being used as an

indicator. No sediment separates from the solution in ampules on

prolonged standing (insoluble salts, ultramarine or prussian blue). A

10 per cent solution is not affected by the addition of an equal volume

of hydrogen sulfide T.S. (heavy metals). Ten cc. portions of a

10 per cent solution remain clear for at least one minute after the

addition of 1 cc. of silver nitrate T.S. (chloride) or of ammonium

oxalate T.S. (calcium). A portion equivalent to 5 Gm. of invert

sugar shows no more sulfate than corresponds to 0.3 cc. of fiftieth-

normal sulfuric acid. A solution equivalent to 5 Gm. of invert sugar

evaporated to dryness and ashed yields a residue weighing not more than

4 mg. A solution equivalent to 5 Gm. of invert sugar yields not more

ammonia than is equivalent to 0.5 cc. of hundredth normal hydrochloric

acid. A solution containing 16 per cent of invert sugar calculated from its

copper reducing power, when examined by means of the polariscope

has a specific rotation of $[\alpha]_{D}^{25}$ between -16 and -18.5.

Dilute exactly 10 cc of the original to exactly 500 cc, transfer 10 cc of this solution to a 250 cc beaker and assay for invert sugar according to the *Methods of Analysis of the Association of Official Agricultural Chemists*, ed 6 pp 571-572 paragraphs 38 and 39 the amount of invert sugar is wit in 5 per cent of the amount claimed. Transfer 50 cc of the prepared solution to a 100 cc standard flask, invert according to the *Method of Analysis A O A C*, ed 6, p 566 paragraph 24c and assay for sucrose according to paragraph 30, page 569 the weight of sucrose is not greater than 4 per cent of the weight of invert sugar found.

IOCAMFEN (SCHERING & GLATZ)—A liquid obtained by the interaction of iodine 10 parts phenol 20 parts and camphor 70 parts, containing about 7.25 per cent free iodine.

This preparation is a dark reddish brown, viscid liquid having a camphoraceous odor. It is insoluble in water, but soluble in all proportions in alcohol, ether, benzene and liquid petrolatum.

The preparation like free iodine interacts with fats and waxes its free iodine entering into combination.

Accurately weigh about 2 Gm of the preparation into a glass stoppered flask and dissolve it in about 25 cc of chloroform. Add about 10 cc of potassium iodide solution (1 in 10) and titrate the free iodine with tenth normal sodium thiosulfate solution using starch T S as an indicator.

IODINATED CASTOR OIL—A 66 per cent solution in oil of an iodine addition product of castor oil. Iodinated castor oil contains about 17 per cent of iodine.

Iodinated castor oil is an oil like liquid, light amber in color having a faint alkaline reaction. It is insoluble in water, soluble in alcohol, chloroform and ether.

When heated it is decomposed and purple vapors of iodine are given off. When heated with alcoholic potash, iodinated castor oil is saponified and potassium iodide formed.

IDOALPHIONIC ACID— $C_{15}H_{12}I_2O_3$ —M W 494.1
— β (4 Hydroxy 3,5 diiodophenyl) α phenylpropionic acid.

Iodoalphonic acid occurs as a white or faintly yellowish, practically odorless and tasteless powder. It is soluble in alcohol and ether, slightly soluble in benzene and chloroform, soluble in both alkali carbonate and hydroxide solutions and insoluble in water. Iodoalphonic acid melts at 157 to 162 C. with decomposition.

Shake about 0.2 Gm of iodoalphonic acid with 2 cc of water and 2 cc of chloroform; the chloroform layer remains colorless (absence of free iodine).

Place about 0.3 Gm of iodoalphonic acid in a 50 cc. glass stoppered cylinder, add 30 cc of water, shake the contents for five minutes, filter through paper, separate portions of 10 cc each of the filtrate, yield a very faint opalescence with 0.5 cc diluted nitric acid and 0.5 cc silver nitrate solution (soluble halides); no color or precipitate on

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IODOBISMUTHITE SODIUM— $BiI_3Na_2 \cdot 6H_2O$ —
M W 998.59—Bismuth sodium iodide hexahydrate.

Iodobismuthite sodium occurs as a red crystalline compound, odorless, or having only a faint acetic or ethyl acetate odor, permanent in dry air and possessing an astringent taste. It yields a clear solution

with one part water; on moderate dilution of the solution, sodium iodobismuthite hydrolyzes to form a black precipitate of bismuth iodide in a finely divided state, while on further addition of water the black precipitate changes to red bismuth oxyiodide. Hydrolysis may be retarded by the addition of acids or alkali iodides. The aqueous solution is neutral or faintly acid to litmus. Iodobismuthite sodium dissolves readily and without decomposition in ethyleneglycol, propylene glycol, glycerin, anhydrous alcohol and ethyl acetate; it is insoluble in absolute ether, chloroform, carbon disulfide, petroleum ether, fixed oils and liquid petrolatum. On heating the product in an oven at 80 to 110 C., it loses water of hydration, with slight decomposition, leaving a maroon colored residue that becomes brown or black on aging, and that changes to red on exposure to moisture.

Add 3 cc. of hydrochloric acid and 25 cc. of water to about 0.5 Gm. of iodobismuthite sodium, add an excess of strong ammonia solution, filter and wash the filter with water. Ignite the filter in a quartz crucible; the residue is yellow. A few drops of the filtrate imparts an intense yellow color to water.

1 Gm. of iodobismuthite sodium with 10 cc. of absolute ether; no residue remains after the evaporation of the solvent. Add 2 cc. of nitric acid to 1.5 Gm. of bath and 1 g solution mee sufficient nit in a 150 cc. the filtrate 1 tions of 5 cc. each. Mix one portion with an equal volume of diluted

precipitate another supernatant is not immediate portion, add

diluted hydrochloric acid no precipitate is formed (silver).

Transfer about 0.4 Gm. of iodobismuthite sodium, accurately weighed, to a wide mouth weighing bottle and heat to constant weight in an oven at 110 C., the loss in weight is not less than 10.5 per cent nor more than 12.5 per cent.

Transfer about 0.2 Gm. of iodobismuthite sodium, accurately weighed, to a beaker, dissolve in 3 cc. of hydrochloric acid and 125 cc. of water, saturate the solution with hydrogen sulfide to precipitate the bismuth as bismuth sulfide, filter in a Gooch crucible, wash with water, alcohol, chloroform, and ether in this order, dry for one hour at 100 C., cool in a desiccator and weigh, repeat the washing with chloroform and ether and the drying at 100° C. until constant weight is attained; the bismuth sulfide is equivalent to not more than 21.8 per cent, nor less than 20.3 per cent bismuth.

Transfer about 0.2 Gm. of iodobismuthite sodium, accurately weighed, to a 250 cc. beaker, add 10 cc. of a solution of acid silver nitrate (prepared by dissolving 1 Gm. of silver nitrate in 20 cc. of water and adding 5 cc. of nitric acid) and then 100 cc. of water, allow to stand two hours, filter, using a filter paper, and wash well with water. Without allowing the precipitate to dry, puncture the filter and, using 100 cc. strong ammonia solution, wash the precipitate into a 250 cc. glass-stoppered Erlenmeyer flask, agitate the solution, then allow the flask and contents to stand two hours, collect the precipitate on a prepared Gooch crucible and wash it with diluted ammonia solution, then with water; dry to constant weight at 100° C. The weight of silver iodide is equivalent to not less than 60 per cent nor more than 63 per cent of iodine. Add 10 cc. of potassium iodide T.S. to the filtrate and heat on the steam bath until most of the ammonia has been removed, filter the solution and collect the precipitate on a prepared Gooch crucible, wash with water, dry to constant weight at 100° C.; the weight of silver iodide is equivalent to not more than 0.7 per cent chloride.

889 59—A solution of iodobismuthite sodium with ethyl aminobenzoate (containing 10 per cent of potassium iodide) and ethyl aminobenzoate

zoate

The specific gravity of iodobismuthite sodium with ethyl aminobenzoate at 25 C ranges from 1.167 to 1.175. The pH of iodobismuthite sodium with ethyl aminobenzoate taken with a quinhydrone electrode ranges from 4.5 to 5.0. The refractive index at 25 C ranges from 1.4609 to 1.4611.

Transfer about 3 cc of iodobismuthite sodium with ethyl aminobenzoate, accurately weighed, to an Erlenmeyer flask, add 3 cc of hydrochloric acid and 125 cc of water, determine the bismuth according to the method outlined under iodobismuthite sodium, each cubic centimeter contains the equivalent of not less than 0.012 nor more than 0.0138 Gm of bismuth. Add 10 cc of a nitric acid silver nitrate solution (prepared by dissolving 1 Gm of silver nitrate in 20 cc of water and adding 5 cc of nitric acid) to about 3 cc of iodobismuthite sodium with ethyl aminobenzoate, accurately weighed, and then add 100 cc of water, allow to stand two hours, filter into a prepared Gooch crucible and wash with very dilute nitric acid (5 cc of diluted nitric acid to make 100 cc.), and dry to constant weight at 100° C. The weight of silver iodide is equivalent to not less than 0.135 nor more than 0.145 Gm of iodine per cubic centimeter.

IODOBISMUTHITE SODIUM. The iodobismuthite sodium in iodobismuthite sodium with ethyl aminobenzoate conforms to the New and Nonofficial Remedies standards for this substance.

ETHYL AMINOBENZOATE. The ethyl aminobenzoate in iodobismuthite sodium with ethyl aminobenzoate conforms to the U S P standards for this substance.

PROPYLENE GLYCOL. The propylene glycol in iodobismuthite sodium with ethyl aminobenzoate conforms to the National Formulary standards for this substance.

IODOBASSID.— $C_{22}H_{42}I_2O_2$ —M W 592.4—Ethyl diiodobassidate

Iodobassid crystallizes in white, odorless and tasteless needles melting at 37 C. It is insoluble in water, slightly soluble in alcohol and very soluble in fatty oils, ether and benzene. Iodobassid is decomposed by exposure to direct light.

The iodine content of iodobassid is from 40.5 per cent to 41.5 per cent.

IODOPYRONE COMPOUND SOLUTION.

Iodopyra et compound solution occurs as a clear, pale yellow, odorless liquid possessing a bitter taste. It is neutral to litmus and is incompatible with mineral acids and heavy metal salts. Its specific

gravity is 1.167 to 1.175. It is neutral to litmus and is incompatible with mineral acids and heavy metal salts. Its specific composition (the

precipitate on a solution of sodium hydroxide and hydrochloric acid is less on a water solution than on a water solution a little at a time

to force out a crystalline precipitate; filter; dry the product under partial vacuum; the melting point of the diethylamine hydrochloride obtained is from 224° to 227° C., with sublimation.

Acidify the alkaline residue remaining in the distilling flask with diluted hydrochloric acid; remove the solution from the flask and evaporate to about one third of its volume. Cool the concentrated solution in ice water for fifteen minutes with occasional shaking, filter and concentrate the filtrate to a syrup. Treat the syrupy residue with 5 cc. of absolute alcohol, neutralize by dropwise addition of sodium hydroxide T.S., filter, wash and finally dilute the filtrate to about 8 cc. with alcohol. Add about 0.5 Gm. of picric acid to the solution, boil, cool and place in an ice chest. Collect the precipitate on a filter, recrystallize from absolute alcohol and dry under partial vacuum; the melting point (Caution!) of the diethanolamine picrate obtained is between 109 and 110 C.

Dilute 20 cc. of iodopyracet compound solution, accurately measured, to 200 cc. in a calibrated flask. Use portions of the diluted solution in the following determinations:

Evaporate 20 cc. of the diluted solution, accurately measured, in a tared platinum dish on a water bath and dry to constant weight at 100 C.; the weight of the residue is equivalent to not less than 48 per cent (W/V) nor more than 51 per cent (W/V) calculated to the original solution. Ash the residue in the presence of sulfuric acid; the

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he fore-
going determination with sulfuric acid. Concentrate the mixture and digest with 10 cc. of sulfuric acid and 0.05 Gm. of selenium metal until clear. Cool, dilute with 100 cc. of water, transfer to the ammonia distillation apparatus and add an excess of 50 per cent sodium hydroxide. Distil into 50 cc. of tenth normal hydrochloric acid and titrate the excess acid with tenth normal sodium hydroxide, using methyl red T.S. as the indicator; the amount of tenth normal hydrochloric acid consumed by the distillate is equivalent to the ammonia derived from both the 3,5-diiodo-4-pyridone N-acetic acid and the diethanolamine.

Transfer a 10 cc. portion of the diluted solution to a 50 cc. beaker, heat gently to boiling and add exactly 12 cc. of silver nitrate T.S. Stir until the precipitate becomes granular, cool in ice water for thirty minutes with occasional stirring; filter through a tared Gooch crucible, using the cold filtrate to wash the beaker, and wash the precipitate with 5 cc. of ice cold water, dry to constant weight at 110° C. To the weight of the precipitate (silver salt of 3,5-diiodo-4-pyridone-N-acetic acid) found, add 0.00135 Gm. as a solubility correction; the weight of silver 3,5-diiodo-4-pyridone acetate found is equivalent to a percent (W/V) calculated to the

idone-N-acetic acid found, calculate the equivalent in cc. of tenth-normal hydrochloric acid for 2 cc. of the original solution. Deduct this number of cc. of tenth normal hydrochloric acid from the number used in the titration of the total ammonia from the Kjeldahl determination. The difference calculated as diethanolamine should be not less than 8.2 per cent (W/V) nor more than 8.7 per cent (W/V).

IODOPYRACET CONCENTRATED SOLUTION.—

... 20 per cent of the
... -acetic acid

See the tests given in the U. S. Pharmacopeia under Iodopyracet Injection, which has about half the strength of iodopyracet concentrated solution, so that the quantities given in the Pharmacopeia must be multiplied by two. See also, so far as they apply, the tests given under iodopyracet compound solution-N. N. R.

ISOBORNYL THIOCYANOACETATE-TECHNICAL.
 $\text{—C}_{13}\text{H}_{19}\text{N}_2\text{OS—}$ M. W. 253.35.—The technical grade of isobornyl thiocyanacetate contains 82 per cent or more of isobornyl thiocyanacetate with other terpenes.

beaker, 5 cc. of two normal alcoholic potassium hydroxide. Cover the beaker with a watch glass and warm on a hot plate for 5 minutes.

Add 1 solution
 litmus p
 solution.

Add 1 cc. of two normal alcoholic potassium hydroxide to 5 cc. of a 10 per cent alcoholic solution of isobornyl thiocyanacetate-technical. A yellow color forms which rapidly changes to a deep orange.

Dissolve 10 Gm. of isobornyl thiocyanacetate-technical in 25 cc. of a saturated solution of potassium hydroxide in methanol and reflux on a steam bath for two hours. Pour the solution into 500 cc. of saturated sodium chloride solution and then acidify with hydrochloric acid. Filter the precipitate on a Buchner funnel, wash with saturated sodium chloride solution and air dry on the filter. Dissolve the precipitate in petroleum ether, add 20 Gm. of anhydrous sodium sulfate, stopper and let stand for several hours. Filter, then evaporate the filtrate to a small volume and cool in an ice bath to effect crystallization. Filter off the crystals, wash with a few cc. of cold petroleum ether and air dry. The isobornyl isolated melts from 200° to 205°.

Determine the nitrogen content of isobornyl thiocyanacetate technical by the Kjeldahl procedure. The amount of nitrogen found is not less than 4.6 per cent, which is equivalent to an isobornyl thiocyanacetate content of 80 per cent.

ISOBORNYL THIOCYANOACETATE LOTION. Pipette 10 cc. of the lotion into a graduated 100 cc. separatory funnel. Add 50 cc. of ether and shake vigorously. Add 10 cc. of alcohol and shake the contents of the flask to break the gel. Allow the funnel to stand and then draw off the lower layer. Dilute the solution remaining in the separatory funnel to 100 cc. with alcohol. Transfer a 10 cc. aliquot to a Kjeldahl flask and determine its nitrogen content, the amount of isobornyl thiocyanacetate technical is not less than 90 nor more than 110 per cent of the claimed amount.

ch possesses an alliaceous odor
 water. On exposure to air and
 color. Its specific gravity at

identity and purity, ash and
 assay as described in the U. S. Pharmacopeia under Iodized Oil except

that the iodine content found is not less than 98 nor more than 112 per cent.

MANNITOL.— $C_6H_{14}O_6$.—M. W. 182.17.—1,2,3,4,5,6-Hexahydroxyhexane.

Mannitol occurs as a white, crystalline substance possessing a sweet taste. It melts at 166° to 168° C. It is freely soluble in water and slightly soluble in alcohol. The refractive index of a 10 per cent aqueous solution at 25° C. is about 1.3478.

Add 5 drops of a saturated aqueous solution of mannitol to 1 cc. of ferric chloride T.S. Add 5 drops of distilled water to a second tube containing 1 cc. of ferric chloride T.S. Add 5 drops of 20 per cent sodium hydroxide solution to each tube: a reddish precipitate of ferric hydroxide forms in the tube with no mannitol, and a yellow precipitate forms in the tube containing mannitol. Shake the tubes vigorously: a clear solution appears in the tube containing mannitol, but the precipitate persists in the other tube. Add 5 more drops of the sodium hydroxide solution: no precipitation occurs in the tube containing mannitol, but a further precipitation of ferric hydroxide takes place in the control.

To 5 cc. of alkaline cupric citrate solution (Benedict's solution) add 1 cc. of a saturated aqueous solution of mannitol. Heat for five minutes in a boiling water bath: no more than a very slight precipitate occurs.

Dry about 0.50 Gm. of mannitol, accurately weighed, at 110° C. for four hours: the loss in weight does not exceed 0.30 per cent.

Ash about 0.50 Gm. of mannitol, accurately weighed; the residue does not exceed 0.05 per cent.

Dissolve 0.1 Gm. of mannitol, accurately weighed, in distilled water and dilute to 100 cc. in a volumetric flask. Transfer 4 cc. of the solution to a 250 cc. Erlenmeyer flask. Add 50 cc. of potassium periodate reagent prepared by mixing 40 cc. of 5 per cent sulfuric acid (29 cc. sulfuric acid per liter) with 60 cc. of 0.1 per cent potassium periodate (1 Gm. of potassium periodate per liter plus 3 to 5 drops of sulfuric acid). Heat the solution on a steam bath for 15 minutes. Cool to room temperature. Add 5 cc. of chloroform and 1 Gm. of potassium iodide. Allow to stand for five minutes and then titrate the solution with fiftieth-normal sodium thiosulfate. Carry out a blank determination in a similar manner using water in place of the mannitol solution. The difference in titration values of the blank and sample is due to the change in periodate concentration due to oxidation of the mannitol. Each cc. of fiftieth-normal sodium thiosulfate used for the oxidation of mannitol is equivalent to 0.003709 Gm. of mannitol: the mannitol content is not less than 98 per cent or more than 102 per cent.

MANNITOL SOLUTION: Determine the density of the mannitol solution by means of a pycnometer. Transfer the mannitol solution from the pycnometer to a volumetric flask of a size calculated to yield a concentration of about 4 mg. of mannitol per 10 cc.

Transfer sufficient solution to contain 4 mg. of mannitol to a 250 cc. Erlenmeyer flask and proceed with the analysis as described in the monograph for mannitol: the mannitol content is not less than 97 per cent or more than 103 per cent of the claimed amount.

MANNITOL HEXANITRATE.— $C_6H_8O_{18}N_6$.—M. W. 452.17.—An explosive compound formed by the nitration of mannitol, a sugar alcohol.

Mannitol hexanitrate tablets are partially soluble in alcohol and in ether.

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on percussion. The operator must be protected by a safety glass screen while determining the amount of mannitol hexanitrate in a sample for

the above test. The sample is dissolved in water, filtered through a dry filter paper into a tared dish and repeat the extraction five times, evaporate the combined filtrates to 3 cc at a temperature not exceeding 35 C, and allow the remaining solution to evaporate spontaneously. Dry the residue over calcium chloride in a vacuum desiccator for eight hours and weigh the mannitol hexanitrate; the amount of mannitol hexanitrate found corresponds to not less than 93 per cent nor more than 107 per cent of the labeled amount.

MEPERIDINE HYDROCHLORIDE. — $C_{15}H_{21}NO_2$ HCl — M. W. 283.79 — Ethyl 1-methyl-4-phenylpiperidine-4-carboxylate hydrochloride

Meperidine hydrochloride occurs as a fine, white crystalline odorless powder, stable in the air at ordinary temperature, soluble in water, acetone and alcohol.

Alcohol, add 10 cc of a 3 per cent alcoholic solution of picric acid, with constant stirring, the solution becomes

the color of the solution is

the amount of picric acid consumed corresponds to not less than 83.5 per cent nor more than 87.5 per cent of ethylmethylphenylpiperidine carboxylate when calculated to the dried substance. Transfer the alkaline aqueous portion from the extraction to a 400 cc. beaker and place on a steam

bath to remove the ether, add 100 cc. of water, followed by the addition of 5 cc. of nitric acid and with continuous stirring, precipitate of silver chlor nitric acid and water, to stant weight at 105° C.; the silver chloride found more than 11.2 per cent, when calculated to the dried substance.

MERALLURIDE SODIUM SOLUTION.—A sterile aqueous solution containing in each cubic centimeter approximately 119 mg. of meralluride ($C_9H_{16}HgN_2O_6C_7H_8N_4O_2$) and 13 mg. of theophylline ($C_7H_8N_4O_2$ —M. W. 180.17), adjusted with sodium hydroxide to a pH of about 7.5 Each 1 cc. of meralluride sodium solution contains the equivalent of 39 mg. of mercury and 48 mg. of theophylline—U. S. P.

Meralluride sodium solution is clear, colorless to pale yellow and odorless and possesses a bitter taste. The pH of the solution is between 7.4 and 7.6 at 25° C. Meralluride sodium solution should be protected from light.

Five cubic centimeters of meralluride sodium solution responds to tests for the presence of mercury, allylsuccinylurea and theophylline given under Meralluride-N. N. R. Evaporate 1 cc. of meralluride sodium solution to dryness in a tared porcelain dish and ignite; the residue responds to tests for sodium.

To 5 cc. of meralluride sodium solution add 0.5 cc. of sodium acetate T.S. and 0.3 cc. of diluted acetic acid; dilute to 10 cc. with water and divide the solution into two portions. Add to one portion 0.2 cc. of sodium sulfide T.S. and compare with the other portion; only a very faint difference in color of the solution tested is noticeable immediately.

Determine the mercury content of 2 cc. of meralluride sodium solution, accurately measured, by the method given under Meralluride-N. N. R.; the amount of mercury found is not less than 95 per cent nor more than 105 per cent of 39 mg. per cubic centimeter.

Determine the theophylline content of 5 cc. of meralluride sodium solution, accurately measured, by the method given under Meralluride-N. N. R.; the amount of anhydrous theophylline found is not less than 95 per cent and not more than 105 per cent of 43.6 mg. per cubic centimeter.

MERCOCRESOLS.—A mixture consisting of equal parts by weight of *secondary*-amyltricresol $CH_3-C_6H_3(OCH(CH_3)C_3H_7)$ and *ortho*-hydroxyphenylmercuric chloride *ortho*- HOC_6H_4HgCl .

Secondary-amyltricresol ($C_{12}H_{18}O$ —F. W. 178.26) is a mixture of isomeric *secondary*-amyl cresols obtained by the reaction of cresol and *sec*-amyl alcohol. It appears as a yellowish liquid, which darkens on exposure to light and air, and possesses a phenol-like odor. It is miscible with the common organic solvents (acetone, alcohol, benzene, chloroform, ether); soluble in solutions of fixed alkalis forming a cloudy solution; slightly soluble in water; soluble in an aqueous solution of 10 per cent acetone and 50 per cent alcohol from which it does not precipitate on addition of water. A saturated aqueous solution is neutral or slightly acid to litmus. It gives no color reaction with ferric chloride T.S. (*cresol*). At a pressure of 5 mm. of mercury not less than 95 per cent distills between 115° and 130° C. The refractive index is 1.5140-1.5190 at 25° C. The specific gravity is 0.95-0.98 at 25° C.

Ortho-hydroxyphenylmercuric chloride (C_6H_4OHgCl —M. W. 329.26) is in alcohol, alkalis, very of 10 per 1° C. The

saturated aqueous solution is slightly acid to litmus. A 0.1 per cent solution in diluted nitric acid yields the following qualitative reactions:

the addition of ammonium sulfide T.S. gives no precipitate within five minutes but on warming over a steam bath a black precipitate is formed; on warming with silver nitrate T.S. it yields a white precipitate soluble in excess strong ammonia solution when treated with an excess of sodium hydroxide T.S. it yields no yellow precipitate (mercuric ion) and the color does not darken (mercurous ion)

o-Hydroxyphenylmercuric chloride gives no color reaction with ferric chloride T.S. It yields not more than 0.1 per cent of residue on ignition. There is no apparent loss of weight on drying in a vacuum over phosphorus pentoxide for 24 hours. The alcohol-insoluble residue does not exceed 2 per cent of ".

Transfer chloride, accurately weighed, to hydrochloric acid and 150 cc. of solution is complete. Saturate the warm solution with hydrogen sulfide and allow it to stand until the precipitated mercuric sulfide has settled. Filter on a Gooch crucible and wash with water, alcohol, ether, carbon disulfide and ether in the order listed. Dry in an oven at 100-110° C. for one half hour and finally cool in a desiccator. The weight of mercuric sulfide found multiplied by 0.8622 is equivalent to a mercury content of not less than 69.5 nor more than 61.6 per cent.

MERCURIC POTASSIUM IODIDE.— K_2HgI_4 —M.W. 787.

Mercuric potassium iodide occurs as yellow crystals, deliquescent in air. It is soluble in alcohol and in potassium iodide T.S. It yields a clear solution with one part of water. When the solution is diluted with much water, mercuric iodide precipitates slowly, but if one fifth of its weight of potassium iodide is previously added to the salt or its concentrated solution, no mercuric iodide separates on dilution. Its aqueous solution is slightly alkaline to litmus. When the salt is heated in a test tube to the point of fusion, it becomes red, but on cooling again assumes a yellow color, at higher temperatures, there is volatilization of mercuric iodide.

Treat about 0.2 Gm. of mercuric potassium iodide with 1 cc. of water and add 1 cc. of chloroform and 0.5 cc. of ferric chloride T.S. the chloroform shows the characteristic color of iodine. Treat about 0.1 Gm. of the salt with 2 cc. of sodium hydroxide T.S. and add a few drops of formaldehyde T.S. a black precipitate of metallic mercury is produced.

Mercuric potassium iodide loses not more than 4 per cent of its weight when dried at 120° C. for four hours.

Transfer about 15 Gm. of mercuric potassium iodide, accurately weighed, to a 100 cc. volumetric flask and dissolve in 15 cc. of water, then dilute to 100 cc. Immediately pipette 10 cc. of the solution into a glass stoppered 250 cc. bottle and add 35 cc. of hydrochloric acid and 5 cc. of chloroform. Titrate the solution with tenth normal potassium iodate (10.761 Gm. in 1,000 cc.) stopper the bottle and shaking the contents

Dissolve about 2.5 Gm. of mercuric potassium iodide, accurately weighed, in about 10 cc. of water, and add sufficient potassium iodide solution to prevent precipitation of mercuric iodide. Introduce the solution and washings into a tared cathode cup and add 10 cc. of 20 per cent sodium hydroxide solution. Pass through the solution a direct electric current, gradually increasing the strength of the current so that at the end of eight minutes it will be 2 to 3 amperes and 7 to 10 volts, stirring the solution by rotating the anode about 500 revolutions per minute. After 40 minutes, wash with distilled water with the aid of a siphon and without interrupting the current, until the current drops to zero. Remove

content of mercuric potassium iodide, calculated to the dry salt, is not less than 25.0 per cent, nor more than 26.0 per cent.

MERTHIOLATE (LILLY).— $C_9H_9HgNaO_2S$.—M. W. 404.83.—Sodium ethylmercurithiosalicylate.

Sodium ethylmercurithiosalicylate occurs as a light cream colored, non-hygroscopic, crystalline powder, having a slight odor. It is stable in air but unstable in sunlight. One part by weight of sodium ethylmercurithiosalicylate

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mercurithiosalicylate: a white precipitate separates. Add a few drops of cupric sulfate T.S. to a 1 per cent solution of sodium ethylmercurithiosalicylate: a green precipitate separates.

Shake 0.5 Gm. of dried substance with 10 cc. of water, accurately weighed,

on standing 48 hours. Dry

to constant weight in a

more than 0.5 per cent in

weight

Transfer about 0.2 Gm. of sodium ethylmercurithiosalicylate, accurately

weighed, to a 100 cc. beaker,

hydrochloric acid and 3 cc. of

of bromine no longer appear.

pletely saturate with hydrogen

Gooch crucible, wash with alcohol

ether; dry to constant weight.

responds to not less than 49.1 per

calculated to the dried substance.

MESTILBOL.— $C_{19}H_{22}O_2$.—M. W. 282.37.—3-*p*-Hydroxy-

phenyl-4-*p*-methoxyphenyl-3-hexene.

Mestilbol occurs as an odorless white crystalline powder which melts

at 100°C. It is soluble in alcohol, ether, and benzene.

solvent: a red colored solution is produced which changes rapidly to

purple (distinction from hexestrol, which gives no color).

Dissolve 10 mg. of mestilbol in 5 cc. of concentrated sulfuric acid:

an orange color is produced which disappears on dilution with water

(distinction from hexestrol and benzestrol, which give no color).

Dry an accurately weighed specimen of mestilbol at 100°C. for four

hours: the loss does not exceed 0.5 per cent. Ignite an accurately weighed

specimen of mestilbol after the addition of concentrated sulfuric acid the sulfated ash residue is not more than 1 per cent.

Transfer 0.1 Gm. of mestilbol to a 100 cc volumetric flask and dilute to the mark with carbon tetrachloride. Transfer 10 cc of the solution to a 250 cc iodine flask fitted with an accurately ground stopper, add the

able.

METHACHOLINE BROMIDE — $C_8H_{18}BrNO_2$ —
M. W. 240.15—Acetyl β methylcholine bromide.—Trimethyl- β -acetoxy-propyl ammonium bromide

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Moisten about 0.1 Gm. of methacholine bromide with a 5 per cent solution of platinum chloride. Small rhombohedral plates are formed (distinction from acetylcholine chloride, which forms needles, and choline chloride, which forms no crystals). Dissolve 0.2 Gm. of methacholine bromide in 2 cc of sulfuric acid; the solution is colorless (readily carbonizable substances).

Dry about 0.5 Gm. of methacholine bromide, accurately weighed, to constant weight at 110 C.; the loss in weight does not exceed 1.5 per cent. Incinerate about 0.5 Gm. of methacholine bromide, accurately weighed, in

add 5 cc. of nitric acid, and finally add water to final volume and mix thoroughly. Filter through a dry filter into a dry flask, rejecting the first filterful; titrate 50 cc. of the filtrate with tenth normal ammonium thiocyanate solution using ferric ammonium sulfate T.S. as an indicator; the amount of bromine is not less than 32.9 per cent nor more than 33.5 per cent.

DE.— $C_{21}H_{27}NO.HCl$.
-diphenyl-3-heptanone-

METHADONE hydrochloride occurs as colorless crystals or as a white crystalline powder, which is odorless and possesses a bitter taste. It is soluble in water, freely soluble in alcohol and in chloroform, practically insoluble in ether, and insoluble in glycerin. It is much more soluble in diluted sulfuric acid than in diluted nitric acid, and is slightly soluble in diluted hydrochloric acid. It is incompatible with alkaline solutions and with syrup of wild cherry U. S. P. It is precipitated from solution by the common alkaloidal reagents. The pH of a 1 per cent aqueous solution of methadone hydrochloride is between 4.5 and 6.5. It melts at 232-235° C. An aqueous solution of methadone hydrochloride, 50 mg. per 100 cc., exhibits an ultraviolet absorption maximum at 2920 Å.

(E $\frac{1\%}{1 \text{ cm.}}$ = 156 \pm 0.1).

Dissolve about 0.1 Gm. of methadone hydrochloride in 10 cc. of water, and add a clear, saturated solution of silver nitrate T.S. to the solution, which is dissolved in 50 cc. of water. A yellow precipitate forms. Filter and dry the residue: the product melts at 232-235° C.

Dissolve about 10 mg. of methadone hydrochloride in 2 cc. of water. Add 2 cc. of methyl orange T.S.: a yellow precipitate forms.

Dissolve about 10 mg. of methadone hydrochloride in 10 cc. of water, add 1 cc. of diluted nitric acid and 1 cc. of silver nitrate T.S.: a white precipitate forms which is soluble in excess ammonia T.S.

Dry about 1 Gm. of methadone hydrochloride in a vacuum desiccator, for 24 hours at 100° C.

Ignite about 0.1 Gm. of the dried substance; the residue does not ignite.

Transfer about 0.5 Gm. of methadone hydrochloride, weighed, to a 250 cc. flask and dissolve it in 50 cc. of water with tenth normal silver nitrate, using 10 drops of methyl orange as the indicator. Each cc. of tenth normal silver nitrate 0.003546 Gm. of chloride: the amount of chloride is not nor more than 10.5 per cent, calculated to the dry substance.

Transfer about 0.1 Gm. of methadone hydrochloride, to a suitable Kjeldahl flask and determine the semimicro method, U. S. P. XIII, p. 672: the amount less than 3.95 nor more than 4.15 per cent, calculated to the dried substance.

Dissolve about 0.15 Gm. of methadone hydrochloride, weighed, in 50 cc. of water in a separatory funnel with ammonia T.S., and extract the methadone base, portions of 40 cc., 20 cc., 20 cc., and 15 cc. of ether, in a beaker and carefully evaporate the ether in a stream of warm air. Dissolve the residue in alcohol and titrate the solution with fiftieth-normal sodium hydroxide T.S. as the indicator. Near 50 cc. of water. Each cc. of fiftieth-normal sodium hydroxide 0.00619 Gm. of methadone base. The amount corresponds to not less than 88.5 nor more than 91.5 per cent of the dried substance.

METHAMPHETAMINE

$C_{10}H_{15}N.HCl$.—M. W. 185.69.—T.

1-2-methylaminopropane.

Methamphetamine hydrochloride occurs

crystalline powder, possessing a bitter taste. It is unaffected by light. It is soluble in alcohol, chloroform and water, but insoluble in ether. Methamphetamine hydrochloride melts between 170° and 175° C. A 1 per cent aqueous solution is neutral or slightly acid to blue litmus paper and has a specific rotation, $[\alpha]_{25/D}$, not less than $+14^{\circ}$ nor more

E.—N,N-di-
hydrochloro-

Methapyrilene hydrochloride occurs as a white, crystalline powder having a faint odor. It melts between 159° and 162° C. It is very soluble in water, freely soluble in alcohol and chloroform, and very slightly soluble in ether and benzene. The free base is obtained as an oil upon the addition of a 5 per cent sodium hydroxide solution to an aqueous solution

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precipitate is formed

Dry about 1 Gm. of methapyrilene hydrochloride, accurately weighed,
at 100 C. for 4 h. per cent.

Char about 0.2 Gm. of the same substance, accurately weighed,
over a low flame continue
ignition until no exceed 0.3
per cent.

Transfer about 0.5 Gm. of dry methapyrilene hydrochloride, accurately weighed, to a 100 cc. volumetric flask. Add 50 cc. of distilled water and 3 cc. of nitric acid. Mix thoroughly, add exactly 25 cc. of 0.1 N silver nitrate and fill to the mark with distilled water. Shake the mixture vigorously and allow the silver chloride to settle out. Transfer exactly 50 cc. of the clear, supernatant liquid into a flask and titrate the excess silver nitrate with 0.1 N ammonium thiocyanate, using ferric ammonium sulfate T.S. as an indicator. Each cc. of 0.1 N silver nitrate is equivalent to 0.003647 Gm. of hydrogen chloride; the amount of hydrogen chloride found is not less than 12.1 nor more than 12.4 per cent.

Transfer 0.1 Gm. of methapyrilene hydrochloride, accurately weighed, to a 100 cc. volumetric flask. Add 50 cc. of distilled water and 3 cc. of nitric acid. Mix thoroughly and transfer to a 100 cc. flask. Dilute to 100 cc. with distilled water. This is the final solution (0.001 per cent).

(E) $\frac{1\%}{1 \text{ cm}} = 623 \pm 6$ and 3050 Å, and a minimum at 2740 Å

Transfer about 0.2 Gm. of dry methapyrilene hydrochloride, accurately weighed, to a separatory funnel. Add 10 cc. of water, 5 cc. of 0.5 N sodium hydroxide and extract with six 20 cc. portions of ether. Collect the ether extract in a separatory funnel and wash with two 5 cc. portions of water. Extract the wash water with 10 cc. of ether and add this ether to the combined ether extracts. Treat the combined ether extracts with 20 cc. of 0.05 N hydrochloric acid, accurately measured, and then successively with 10 cc. and 5 cc. of water. Combine the acid and water extracts, heat gently until the ether is removed and titrate the excess acid with 0.02 N sodium hydroxide, using a 0.1 per cent alcoholic solution of aurin as an indicator. 1 cc. of 0.02 N acid is equivalent to 0.005227 Gm. of methapyrilene hydrochloride; the amount of methapyrilene hydrochloride contained in the sample is not less than 95 per cent.

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METHENAMINE TETRAIODIDE. — $C_6H_{12}I_4N_4$ —
M. W. 647.89 — Hexamethylenetetramine tetraiodide

Methenamine tetraiodide is a red powder, having a slight, but characteristic, odor and taste. When heated (caution!) to $138^\circ C.$, it decomposes with violence.

Methenamine tetraiodide is slightly soluble in acetone, alcohol, chloroform, carbon disulfide and ether (with partial decomposition). It is almost insoluble in water, but dissolves with decomposition in aqueous solutions of alkali iodides and of sodium thiosulfate and in diluted hydrochloric acid.

Heat 5 Gm. of methenamine tetraiodide with 15 cc. of diluted sulfuric acid: first vapors of iodine (recognized by their color and effect on starch paper) are evolved, later, formaldehyde is given off (recognized by its odor and the blackening of paper moistened with silver ammonium nitrate).

The iodine content of methenamine tetraiodide is 78.5 per cent.

METHIODAL SODIUM. — $CH_2I\text{NaO}_3S$ — M. W. 244.0 —
The sodium salt of mono-iodomethanesulfonic acid

Methiodal sodium occurs as a white, crystalline, odorless powder possessing a slight saline taste followed by a sweetish after taste; it is very soluble in methyl alcohol, slightly soluble in ethyl alcohol, practically insoluble in acetone, benzene and ether, the aqueous solution is neutral to litmus, on exposure to light it decomposes, turning to a yellow color.

Fuse about 0.5 Gm. of methiodal sodium with 5 Gm. of powdered anhydrous sodium carbonate in a nickel crucible until decomposed. Allow the crucible and contents to cool, dissolve the residue in 20 cc. of water, filter the mixture through paper and divide the filtrate into two portions. To one portion add an excess of diluted hydrochloric acid followed by the addition of a few drops of freshly prepared 10 per cent sodium nitrite solution and finally a few drops of chloroform and agitate the mixture: a deep violet color is assumed by the chloroform. To the other portion add a few drops of freshly prepared sodium nitroprusside T.S. a deep violet color results. To about 0.1 Gm. of methiodal sodium dissolved in 5 cc. of water, add an excess of acetic acid, followed by the addition of an equal volume of cobalt uranyl acetate T.S. a yellow crystalline precipitate results. Dissolve about 1 Gm. of methiodal sodium in 25 cc. of water; separate portions of 5 cc. each yield no opalescence or at most a slight opalescence with 1 cc. of diluted nitric acid and 1 cc.

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METHIONINE.—DL-Methionine.— γ -Methylthiol- α -amino-butyric acid.— $C_5H_{11}NO_2S$.—M. W. 149.21.

DL-Methionine occurs as white, crystalline platelets or a powder, having a faint odor. It is soluble in water, dilute acids and dilute alkalis; very slightly soluble in alcohol; and practically insoluble in ether. A 1 per cent aqueous solution of DL-methionine exhibits a pH in the range 5.6-6.1, and is optically inactive.

Dissolve 4.5 Gm. of DL-methionine in 150 cc. of water. The solution is clear and colorless. To 25 cc. of this solution add 1 cc. of diluted hydrochloric acid and 2 cc. of barium chloride T. S. The turbidity is less than that shown by 0.4 cc. of 0.02 N sulfuric acid diluted to 25 cc., and treated in a similar manner (*sulfate*). To another 25 cc. portion add 1 cc. of nitric acid and 1 cc. of silver nitrate T. S. The turbidity is not more than that obtained when 0.2 cc. of 0.02 N hydrochloric acid is diluted to 25 cc., and treated in the same manner (*chloride*). Add 1 cc. of 1 N sodium hydroxide and 1 drop of Nessler's reagent T. S. to 25 cc. of the DL-methionine solution; the color developed is less than that produced by 25 cc. of a solution containing 0.0125 mg. of ammonium chloride (*ammonium salts*). Add 1 cc. of 4 N hydrochloric acid to 25 cc. of the solution and then add 10 cc. of hydrogen sulfide T. S. The color produced is less than that obtained when 15 cc. of standard lead solution (*U. S. P. XIII*) is diluted to 25 cc., acidified and treated with hydrogen sulfide T. S. (*heavy metals*). To the solution containing DL-methionine, used in the test for heavy metals, add 2 cc. of ammonia T. S. the green color obtained is no darker than that produced by treating the blank from the heavy metals test with 1 cc. of ferric chloride solution containing about 0.05 mg. iron (made by diluting 1 cc. of ferric chloride colorimetric solution, *U. S. P. XIII*, to 200 cc.), mixing, and adding 2 cc. of ammonia T. S.

Add about 25 mg. of dry DL-methionine to about 1 cc. of saturated solution of anhydrous copper sulfate in sulfuric acid the appearance of a yellow color indicates methionine.

Dissolve about 5 mg. of DL-methionine in 5 cc. of water and then add in succession, shaking after each addition, 1 cc. of 5 N sodium hydroxide, 1 cc. of 1 per cent glycine, and 0.3 cc. of 10 per cent sodium nitroprusside (freshly prepared). Keep at 35-40 C. for 10 minutes, and then cool in an ice-bath for 2 minutes. Add 2 cc. of 20 per cent hydrochloric acid and shake the mixture: the appearance of a reddish purple color indicates methionine.

Dry about 100 mg. of DL-methionine, accurately weighed, at 100 C. for 4 hours.

Char about 100 mg. of DL-methionine, accurately weighed, over a low flame. Cool, and ignite until no carbon remains. the residue does not exceed 0.05 per cent.

Transfer about 0.1 Gm. of dry DL-methionine, accurately weighed, to a semi-micro Kjeldahl flask and digest with 5 cc. of sulfuric acid, 2 Gm. of potassium sulfate, 0.2 Gm. of copper sulfate and 1 cc. of 30 per cent hydrogen peroxide. Dilute the clear solution to 10 cc., make alkaline with 40 per cent sodium hydroxide, and distil the ammonia into 50 cc. of 0.02 N sulfuric acid. Titrate the excess acid with 0.02 N sodium hydroxide, using methyl red T. S. as an indicator: the nitrogen content is not less than 9.2 nor more than 9.5 per cent.

Weigh, accurately, about 0.3 Gm. of DL-methionine, transfer quantitatively to a 100 cc. volumetric flask and fill to the mark with distilled water. Transfer a 5 cc. portion of the solution to an Erlenmeyer flask and add 2 cc. of phosphate buffer (7 volumes of 1 M K_2HPO_4 and 3 volumes of 1 M KH_2PO_4) and 2 cc. of iodine solution, approximately 0.1 N. Permit the mixture to stand for about 15 minutes and then remove the excess iodine with 0.1 M sodium thiosulfate solution, using starch-potassium iodide T. S. as an indicator. Add 25 cc. of 2 N hydrochloric acid and titrate the iodine liberated with 0.025 N sodium thiosulfate. Perform a blank determination on 5 cc. of the DL-methionine solution as follows: add 1 cc. of 6 N hydrochloric acid and enough 0.1 M potassium iodate solution to give a persistent yellow color. Allow the solution to stand for about 15 minutes and then add 1 cc. of 5 N potassium iodide solution. Add about one-half the sodium hydroxide

remainder of the sodium hydroxide and 3 cc of the phosphate buffer. Add 2 cc of 5 N potassium iodide solution and allow to stand for 10 minutes. Remove the mixture, add 2 cc of 2 N hydrochloric acid, and determine the amount of iodine by the method described in the monograph on potassium iodide. 0.001865 Gm of potassium iodide is equivalent to 0.001865 Gm of metrazol.

TABLETS. The pulverized tablets respond to the identification tests and assay described in the monograph on DL-methionine. Each tablet should contain not less than 95 nor more than 105 per cent of the claimed amount of DL-methionine.

METRAZOL.— $C_6H_{10}N_4$ —M W. 138.17—Pentamethylene-tetrazol

Metrazol occurs as biaxial, optically negative, white crystals that are freely soluble in water. It melts at 57.58°C.

To 10 cc of a 10 per cent aqueous solution of metrazol add 10 cc of saturated mercuric bichloride solution; a white precipitate results, which may be recrystallized from hot water or alcohol to yield crystals melting at 177-178°C. and leaving not more than 0.1 per cent of ash on incineration.

Transfer about 0.2 Gm of metrazol, accurately weighed, to a wide-mouth weighing bottle, allow to stand over calcium chloride, the loss in weight is not more than 0.1 per cent.

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as directed in *U.S.P. XIII*, p. 27, in the monograph on Dried Aluminum Hydroxide Gel, beginning with the words, "... add 3 drops of methyl red T.S. . . ." Save the filtrate and washings for the magnesium determination described later. The amount of aluminum oxide is not less than 45.0 nor more than 55.0 per cent of the labeled amount of dried aluminum hydroxide gel.

To the combined filtrate and washings saved for the magnesium determination, add 1 Gm of dibasic ammonium phosphate $((\text{NH}_4)_2\text{HPO}_4)$ and then add 2 cc. of ammonia T.S., dropwise and with constant stirring a crystalline precipitate forms. Allow the mixture to stand for 15 minutes,

burner, cool and weigh the magnesium oxide formed; the amount of magnesium oxide is not less than 18.0 nor more than 22.0 per cent of the labeled amount of magnesium trisilicate.

Transfer the filter paper containing the precipitate saved from the aluminum oxide determination to a tared platinum crucible and proceed with the assay for silica as directed in *U.S.P. XIII*, p. 300, in the monograph on Magnesium Trisilicate, beginning with the words, "Heat to dryness . . ." The amount of silicon dioxide is not less than 40.5 nor more than 49.5 per cent of the labeled amount of magnesium trisilicate.

NAPHAZOLINE HYDROCHLORIDE.— $\text{C}_{14}\text{H}_{14}\text{N}_2\text{HCl}$.—M. W. 246.73.—2(1-Naphthyl-methyl)imidazoline hydrochloride.

Naphazoline hydrochloride occurs as a white, odorless, crystalline powder possessing a bitter taste. It is freely soluble in water and in alcohol, very slightly soluble in chloroform and practically insoluble in benzene and in ether.

It melts at 155° to 160° C. A 1 per cent solution in water has a pH of 4.5.

Transfer about 0.2 Gm. of naphazoline hydrochloride, accurately weighed, to a tared 100-cc. volumetric flask, add 5 cc. of water, shake to dissolve, add 5 cc. of 10 per cent sodium hydroxide solution, dilute to 100 cc. with water, and mix thoroughly. Transfer 5 cc. of this solution to a 10-cc. volumetric flask, add 5 cc. of 10 per cent sodium hydroxide solution, dilute to 10 cc. with water, and mix thoroughly. Add 1 drop of 1 per cent solution of methyl red to the 10-cc. solution, and titrate with 0.01 N sodium hydroxide solution until the color changes from red to yellow. The amount of naphazoline hydrochloride is not less than 98.0 nor more than 102.0 per cent of the labeled amount.

Transfer about 0.2 Gm. of naphazoline hydrochloride, accurately weighed, to a tared 100-cc. volumetric flask, add 5 cc. of water, shake to dissolve, add 5 cc. of 10 per cent sodium hydroxide solution, dilute to 100 cc. with water, and mix thoroughly. Transfer 5 cc. of this solution to a 10-cc. volumetric flask, add 5 cc. of 10 per cent sodium hydroxide solution, dilute to 10 cc. with water, and mix thoroughly. Add 1 drop of 1 per cent solution of methyl red to the 10-cc. solution, and titrate with 0.01 N sodium hydroxide solution until the color changes from red to yellow. The amount of naphazoline hydrochloride is not less than 98.0 nor more than 102.0 per cent of the labeled amount.

Transfer about 0.2 Gm. of naphazoline hydrochloride, accurately weighed, to a tared 100-cc. volumetric flask, add 5 cc. of water, shake to dissolve, add 5 cc. of 10 per cent sodium hydroxide solution, dilute to 100 cc. with water, and mix thoroughly. Transfer 5 cc. of this solution to a 10-cc. volumetric flask, add 5 cc. of 10 per cent sodium hydroxide solution, dilute to 10 cc. with water, and mix thoroughly. Add 1 drop of 1 per cent solution of methyl red to the 10-cc. solution, and titrate with 0.01 N sodium hydroxide solution until the color changes from red to yellow. The amount of naphazoline hydrochloride is not less than 98.0 nor more than 102.0 per cent of the labeled amount.

It is not less than 14.15 per cent of the dried substance.

Transfer about 0.2 Gm. of naphazoline hydrochloride, accurately weighed, to a tared 100-cc. volumetric flask, add 5 cc. of water, shake to dissolve, add 5 cc. of 10 per cent sodium hydroxide solution, dilute to 100 cc. with water, and mix thoroughly. Transfer 5 cc. of this solution to a 10-cc. volumetric flask, add 5 cc. of 10 per cent sodium hydroxide solution, dilute to 10 cc. with water, and mix thoroughly. Add 1 drop of 1 per cent solution of methyl red to the 10-cc. solution, and titrate with 0.01 N sodium hydroxide solution until the color changes from red to yellow. The amount of naphazoline hydrochloride is not less than 98.0 nor more than 102.0 per cent of the labeled amount.

10 cc) of ether, wash the combined ether extracts with two 5 cc portions of water, extract the water washings with two 10 cc portions of ether and combine these extracts with the main ether extract. Evaporate the ether solution contained in a beaker, to near dryness on a water bath and complete the removal of ether in a stream of cool air, add 10 cc of neutral alcohol to dissolve the residue dilute to about 50 cc with water and titrate with twentieth normal hydrochloric acid, using methyl red TS as the indicator. Each cubic centimeter of twentieth normal hydrochloric acid is equivalent to 0.01234 Gm of naphazoline hydrochloride the naphazoline hydrochloride content found is not less than 97.0 per cent.

NIKETHAMIDE.— $C_{10}H_{14}N_2O$ —M W 178.23—The diethylamide of nicotinic acid

Nikethamide occurs as a clear, colorless to very pale yellowish somewhat viscous liquid, possessing a slight characteristic aromatic odor and a peculiar bitter taste. Nikethamide is miscible in all proportions with water, alcohol and ether. The refractive index of nikethamide is 1.522 to 1.524 at 25° C, the specific gravity is not less than 1.058 nor more than 1.066 at 25° C. The pH of a 25 per cent aqueous solution (W/V) of nikethamide made with freshly boiled and cooled distilled water is not below 6.0 or above 6.5, as determined by means of a glass electrode. Nikethamide freezes on standing in the cold and melts at from 20 to 26° C, it resolidifies easily when cooled provided some fragmentary crystals are present. Nikethamide boils at 128° to 129° C at 3 mm of mercury, at 158° to 159° C at 10 mm. of mercury and at about 296° to 300° C, with some decomposition at one atmosphere.

Dissolve about 3.0 Gm of nikethamide in 10 cc of 10 per cent sodium hydroxide solution and warm on a water bath for thirty minutes the solution yields the odor of diethylamine. Allow the solution to cool acidify with diluted hydrochloric acid to a pH of 3.6 (slightly acid to congo red), collect the fine, white precipitate on a filter, wash with water and recrystallize from 5 cc of water, collect on a filter and dry at 100° C the nicotinic acid obtained melts at 235-238° C.

Heat a few drops of nikethamide with 1 Gm of sodium carbonate a strong odor of pyridine results.

Dissolve 10 Gm of nikethamide in 90 cc of water the solution is clear, nearly colorless and free from the odor of pyridine it yields only a faint odor of diethylamine. The solution will respond to the following tests. Add to 5 cc of solution 5 cc. of normal hydrochloric acid and

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tion, extract twice in a separatory funnel with 20 cc portions of a mixture of 3 parts of chloroform and 1 part of isopropyl alcohol, combine the extracts, filter, evaporate to dryness on a steam bath and dissolve the dry residue in 10 cc of boiling water. When the solution is cool add 0.1 cc of tenth normal sodium hydroxide and 1 drop of phenolphthalein TS the solution turns red (nicotinic acid).

Warm 1.0 Gm of nikethamide for one hour with 3 cc of diluted hydrochloric acid and 6 cc of water, cool and add 5 cc of sodium hydroxide TS the solution yields no distinct yellow color (foreign organic impurities).

A solution made by dissolving 1 Gm of nikethamide in 5 cc of carbon disulfide is clear (water).

Ash 1 Gm of nikethamide the residue is not more than 0.5 mg

Transfer 25 mg. to 50 mg. of nikethamide, accurately weighed, to a 50 cc. Kjeldahl digestion flask and add 1 cc. of water and 1 cc. of concentrated sulfuric acid. Heat the mixture gently until most of the water has been removed and continue heating vigorously for fifteen minutes; cool, add 3 cc. of water, transfer to a micro Kjeldahl distilling apparatus, add 5 cc. of sodium hydroxide solution (1:1) and distil into a flask containing 10 cc. of 2 per cent boric acid solution colored with methyl red solution (1 drop in each 20 cc.). Titrate the solution with fiftieth normal sulfuric acid to a pink color, matched against a prepared blank. Each cubic centimeter of fiftieth normal sulfuric acid is equivalent to 3.565 mg. of nikethamide. The amount of nikethamide found should be not less than 99 nor more than 100.5 per cent.

NITROFURAZONE. — $C_8H_6O_4N_4$. — M. W. 198.15. — 5-Nitro-2-furaldehyde semicarbazone

Nitrofurazone occurs as an odorless, lemon-yellow colored crystalline powder, which turns brown-black and decomposes at from 236 to 240 C. It is nearly tasteless but develops a bitter aftertaste. It is slightly soluble in alcohol (1:590), in propylene glycol (1:350) and in polyethylene glycol mixtures; very slightly soluble in water (1:4200); practically insoluble in ether. The crystals tend to darken on prolonged exposure to light. When dissolved in water, 1 mg. per 100 cc., nitrofurazone

furazone dissolves and the solution is colored dark orange-red.

Place about 50 mg. of nitrofurazone in a 50 cc. flask, add 1 Gm. of granular zinc, 10 cc. of alcohol and 20 cc. of diluted sulfuric acid. Heat on a steam bath the nitrofurazone dissolves slowly and the solution becomes practically colorless.

Dry about 0.5 Gm. of nitrofurazone, accurately weighed, at 100 C. for one hour the loss in weight does not exceed 0.1 per cent.

Char about 0.5 Gm. of nitrofurazone, accurately weighed; cool, moisten with sulfuric acid and finally ignite the residue does not exceed 0.05 per cent.

The micro-mg. Weigh 1 liter free at optical as 34. Use a

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alcohol with 95 cc. of water. Calculate the $E_{1\%}^{1\text{cm}}$ values for nitrofurazone from the data obtained. The observed values of E are a linear function of the concentration and the values of $E_{1\%}^{1\text{cm}}$ calculated for each concentration average $795 \pm 2\%$.

ORIDINE (LILLY). — The calcium salt of the iodized fatty acids of cottonseed oil.

The salt is a light brown powder, nearly odorless and tasteless. It is almost insoluble in water, benzene, ether and alcohol, and slightly soluble in chloroform and carbon tetrachloride.

Mix 1 Gm. of the calcium salt of the fatty acids with 20 cc. of water and filter; the filtrate becomes but slightly opalescent on the addition of silver nitrate T.S. (soluble iodides).

Mix about 0.5 Gm. of the calcium salt of the fatty acids, accurately weighed, in a nickel crucible with a mixture of four parts of powdered

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amount of iodine can be calculated according to the formula

$$x = \frac{7327 w + a - k}{293}$$

where w equals combined weight of silver iodide and silver chloride,
 x equals weight of silver iodide and $(w-x)$ equals weight of silver
chloride by this method contains not less than 23 nor more than 25 per
cent of iodine (Chlorine is used in the manufacture so that the finished
product contains from 1 to 3 per cent of combined chlorine)

ORTHOFORM.— $C_8H_9NO_3$ — M W 167.16 — Methyl
m-amino-*p*-hydroxybenzoate

Orthoform occurs as a fine, white, crystalline powder, neutral in
reaction, melting at from 141 to 143 C., odorless and tasteless. It is
almost insoluble in water, freely soluble in alcohol and soluble in ether.
It is decomposed, by boiling with water or by warming with alkalis or
their carbonates, into methyl alcohol and *p*-hydroxy *m*-aminobenzoic acid
or its alkali salt. When crystallized from chloroform it sometimes
assumes the form of white crystals, melting at from 110 to 111 C. and
returning on melting to the ordinary form.

OXIDIZED CELLULOSE.— $(C_6H_8O_6)_n$ — Absorbable
cotton or gauze—Cellulosic acid

Oxidized cellulose, in the form of gauze or cotton, is slightly off
white in color, is acid to the taste and possesses a slight charred odor.
It is soluble in dilute alkali but insoluble in acid and water. It reduces
Fehling's solution slowly on standing but rapidly on heating (*distinction
from cotton*).

The yellow solution obtained by vigorously shaking for one minute 0.2
Gm. of oxidized cellulose in 10 cc. of 1 per cent aqueous sodium hydroxide
solution, followed by the addition of 10 cc. of water, shows only a few
fibers or foreign particles and only a slight haze. The presence of some
swollen fibers may be tolerated if such fibers disappear on standing for
ten minutes. Addition of excess acid to the prepared solution causes a
white, flocculent precipitate.

The moisture content of a 0.2 Gm. sample of oxidized cellulose, when
dried in a vacuum at 50° C. over phosphorus pentoxide for 24 hours does
not exceed 15 per cent.

The residue on ignition of an accurately weighed specimen of oxidized
cellulose does not exceed 0.15 per cent of the weight of the gauze or
cotton.

Place 0.5 Gm. of oxidized cellulose weighed to the nearest milligram,

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cc. of tenth normal sodium hydroxide is equivalent to 0.0045 Gm. of carboxyl group. The carboxyl content is not less than 16 nor more than 22 per cent, calculated on the dry basis.

Place 1 Gm. of oxidized cellulose, weighed to the nearest milligram, in a 500 cc. Kjeldahl flask. Arrange a 125 cc. Erlenmeyer flask, containing 50 cc. of 4 per cent boric acid solution and 6 drops of mixed indicator (1 part of 0.1 per cent methyl red T.S. and 4 parts of 0.1 per cent bromocresol green T.S.), beneath the condenser of the distillation apparatus so that the tip of the condenser is well below the surface of the boric acid solution. Add to the Kjeldahl flask containing the sample, 1 Gm. of Devarda's alloy (50 per cent copper, 45 per cent aluminum, and 5 per cent zinc), 100 cc. of ammonia free distilled water, a small lump of paraffin wax, and 100 cc. of 5 per cent sodium hydroxide solution. Connect the Kjeldahl flask to the condenser by a suitable trap bulb. Heat the mixture in the flask until 45-50 cc. of distillate has collected in the receiver. Rinse the condenser and titrate the boric acid solution with tenth normal sulfuric acid to a pale pink endpoint. Correct the titration by a blank run on the reagents in identical fashion. The nitrogen content should not be more than 0.5 per cent, calculated on the dry basis.

To 1 Gm. of oxidized cellulose in a 500 cc. Florence flask, add 120 cc. of one normal sulfuric acid and a few glass beads. Connect the reaction flask to an apparatus, arranged for distillation, with a dropping funnel filled with distilled water entering the flask. Transfer 10 cc. of a sodium bisulfite solution (13.7 Gm. of sodium bisulfite, or 12.5 Gm. of sodium metabisulfite per liter in water) into a receiver so that the condenser outlet is submerged in the bisulfite solution. The reaction flask is heated to boiling and during distillation, distilled water is added to the reaction flask from the dropping funnel at such a rate that the volume of the contents of the reaction flask is not appreciably altered. Carry on the distillation for one hour, collecting 250-300 cc. of distillate. Cool the distillate, if warm, and allow it to stand for 15 minutes to insure complete reaction of the bisulfite and formaldehyde. Add 1 cc. of starch T.S. and destroy the excess bisulfite by addition of tenth-normal iodine until a blue color is obtained. Discharge the blue color with a drop or two of tenth normal sodium thiosulfate. Add 5 cc. of saturated sodium bicarbonate solution and titrate the liberated bisulfite with tenth normal iodine. As the endpoint is approached, signaled by the very slow consumption of iodine, 0.5 cc. portions of half normal sodium carbonate are added, which discharge the blue color. The endpoint is reached when 1 cc. of the sodium carbonate solution does not discharge the blue color over a period of half an hour. Too great an excess of sodium carbonate is to be avoided since at high pH the iodoform reaction may take place with an increased consumption of iodine. Each cc. of tenth normal iodine is equivalent to 0.0015 Gm. of formaldehyde. The formaldehyde content should not exceed 0.5 per cent of the weight of oxidized cellulose calculated on the dry basis.

OXYQUINOLINE BENZOATE.—8-Hydroxyquinoline benzoate.— $C_{11}H_7NO \cdot C_7H_5O_2$ —M. W. 267.27.—A compound consisting of a molecule of 8-hydroxyquinoline and a molecule of benzoic acid.

Oxyquinoline benzoate occurs as a yellowish white, crystalline powder, possessing a characteristic odor and taste. It is slightly soluble in water; freely soluble in alcohol, benzene and ether; soluble in vegetable and mineral oils. The pH of a saturated aqueous solution of oxyquinoline benzoate is about 4.0. It melts between 61° and 62° C.

Dissolve about 0.1 Gm. of oxyquinoline benzoate in 20 cc. of benzene and extract with two successive 5 cc. portions of sodium bicarbonate T.S. (collect the extracts for a later test). Wash the benzene layer with two portions of water and discard the washings. Dilute about 1 cc. of the benzene layer to 5 cc. with additional benzene. Add 5 cc. of water, 2 drops of ferric chloride T.S. and shake the mixture; an emerald-green color develops immediately in the water layer. Evaporate the remainder of the benzene solution in a stream of air; the melting point of the residue is from 71° to 74° C. Acidify the sodium bicarbonate extract. Collect the

precipitate on a filter and wash and air-dry it the product melts at temperatures from 121° to 123° C and responds to tests for benzoic acid. Ignite about 0.5 Gm of oxyquinoline benzoate, accurately weighed the residue is not more than 0.2 per cent.

Transfer about 0.3 Gm of oxyquinoline benzoate to a suitable separatory funnel, add 25 cc. of benzene and 10 cc of diluted hydrochloric acid, stopper the separator and shake the mixture. Let the funnel stand until the layers separate cleanly and draw off the aqueous layer into a second separatory funnel. Rinse the benzene layer with two 5 cc portions of water, combining the washings with the aqueous extract. To the second funnel add 25 cc of benzene stopper and shake vigorously. Let the funnel stand until the layers separate cleanly, and draw off the aqueous layer into a third separatory funnel. Wash the benzene layer in the second funnel with two 5 cc portions of water and combine them with the aqueous extract. Then (A) transfer the acid aqueous extract containing about 500 cc stoppered in a 500 cc stoppered flask, stopper the flask, let stand 15 minutes, cool in an ice bath, add 10 cc of potassium iodide and titrate the excess iodine with 0.1 N sodium thiosulfate solution. Each cc of 0.1 N sodium thiosulfate is equivalent to 0.003627 Gm of 8-hydroxyquinoline. The amount of 8-hydroxyquinoline found is not less than 51 nor more than 55 per cent. (B) Combine the benzene layer from the second separatory funnel with that in the first. Rinse the second funnel with 5 cc of benzene followed by 10 cc of water, combining both washings in the first separatory funnel. Add exactly 25 cc of 0.1 N sodium hydroxide to the funnel containing the benzene and water washings stopper and shake thoroughly. Allow the layers to separate cleanly and draw off the aqueous layer into a beaker. Wash the benzene in the funnel with two 5 cc portions of water, combining the washings with the aqueous layer in the beaker. Strate the acid the per cent.

excess iodine with 0.1 N sodium thiosulfate solution. Each cc of 0.1 N sodium thiosulfate is equivalent to 0.003627 Gm of 8-hydroxyquinoline. The amount of 8-hydroxyquinoline found is not less than 51 nor more than 55 per cent. (B) Combine the benzene layer from the second separatory funnel with that in the first. Rinse the second funnel with 5 cc of benzene followed by 10 cc of water, combining both washings in the first separatory funnel. Add exactly 25 cc of 0.1 N sodium hydroxide to the funnel containing the benzene and water washings stopper and shake thoroughly. Allow the layers to separate cleanly and draw off the aqueous layer into a beaker. Wash the benzene in the funnel with two 5 cc portions of water, combining the washings with the aqueous layer in the beaker. Strate the acid the per cent.

PAPAVERINE— $C_{20}H_{21}NO_4$ —M W 339.38—An alkaloid obtained from opium, belonging to the benzyl isoquinoline group (not a morphine derivative).

Papaverine occurs in fine, white rhombic prisms or needles or sometimes in scales. It is odorless and tasteless. It is nearly insoluble in cold water, slightly soluble in alcohol, ether, chloroform and benzene if cold and somewhat more soluble in these liquids when hot but deposited by them on cooling, and soluble in warm petroleum ether and in acetone. It melts at 147° C.

If about 10 mg of papaverine is dissolved in 10 cc of water containing a few drops of diluted hydrochloric acid, and a few drops of potassium ferricyanide TS is added, a lemon yellow precipitate of

brown (distinction from morphine and its esters, which give purple or violet colors). If 10 mg of papaverine is dissolved in 0.2 cc of sulfuric acid the solution should not be colored more deeply than a very faint pink or brown (limit of cryptopine thebaine or of other organic impurities). If 10 mg of papaverine is dissolved in 10 cc of water containing a few drops of hydrochloric acid a few drops of a saturated aqueous solution of iodic acid added, and the mixture shaken with chloroform the chloroform layer should not be colored violet (morphine).

If 0.2 to 0.3 Gm. of papaverine is weighed dissolved in 20 cc of warm water containing a few drops of diluted hydrochloric acid the solution cooled, 1 cc of freshly prepared potassium ferricyanide TS added the mixture agitated, allowed to stand overnight and filtered the

filtrate made alkaline with ammonia water, shaken with several successive portions of ether, the ether solutions combined, washed with water, evaporated, the residue dried at 100 C. and weighed, the weight should not amount to more than 2 per cent of the weight taken (*limit of foreign opium alkaloids*).

PARA-AMINOHIPPURIC ACID.— $C_9H_{10}N_2O_3$.—M.W. 194.19.—4-aminobenzoylglycine.—The N-acetic acid amide of para-aminobenzoic acid.

Para-aminohippuric acid occurs as a white, crystalline powder. It melts at 197.5° to 199° C. It is sparingly soluble in water and alcohol, and very slightly soluble in benzene, chloroform and ether.

Dissolve 0.1 Gm. of p-aminohippuric acid in 50 cc. of water. Add to 5 cc. of this solution 0.5 cc. of diluted hydrochloric acid and 0.5 cc. of 10 per cent sodium nitrite, then add 10 cc. of diluted ammonia solution containing 0.2 Gm. of β -naphthol: a red color develops in the solution.

Place 50 mg. of p-aminohippuric acid in a test tube and add 0.5 cc. of potassium iodide T.S., followed by 2 cc. of water. Add 1 cc. of 5 per cent sodium hypochlorite solution: a red color develops in the solution (*distinction from p-aminobenzoic acid*).

Add 0.45 Gm. of p-aminohippuric acid, 0.2 Gm. of freshly fused sodium acetate, 0.25 Gm. of benzaldehyde and 0.75 Gm. of acetic anhydride to a 25 cc. Erlenmeyer flask. Place on a hot plate and shake the flask constantly until the material becomes liquid. Remove the flask immediately, cool, suspend in 10 cc. of water and filter. Wash the crystals with about 10 cc. of alcohol and then with 10 cc. of ether: the dry crystals melt at 236° to 238° C.

Dissolve 1 Gm. of p-aminohippuric acid in 10 cc. of normal sodium hydroxide solution. Add to 25 cc. of the solution 5 cc. of 10 per cent sodium hypochlorite solution and acidify with 0.5 cc. of 10 per cent sodium hypochlorite solution. The solution is produced than of lead as lead nitrate has been added.

Render 10 cc. of the original solution slightly alkaline and pass hydrogen sulfide through it for 10 minutes.

Add 30 cc. of distilled water to 5 cc. of the original solution than corresponds to 0.2 cc. of by the U. S. P. test.

Dissolve 0.5 Gm. of p-aminohippuric acid in a mixture of 5 cc. of nitric acid and 15 cc. of distilled water, the solution shows no more chloride than corresponds to 0.1 cc. of fiftieth-normal hydrochloric acid when treated by the U. S. P. test.

Dry 0.25 Gm. of p-aminohippuric acid, accurately weighed, at 110° C. for two hours: the loss in weight does not exceed 0.25 per cent. Ash about 0.25 Gm. of p-aminohippuric acid, accurately weighed, the amount of residue is not more than 0.05 per cent.

Weigh accurately 0.1 Gm. of p-aminohippuric acid, accurately weighed, and dilute to volume in a 250 cc. beaker with 10 per cent hydrochloric acid. The cooled solution standardized again with 0.0194 Gm. of p-aminohippuric acid is not less than 98 per cent.

STERILE SOLUTION.—ampul solution of p-aminohippuric acid not less than 7.6

Dilute 10 cc. of the solution. Transfer 50 cc. of the diluted solution to analyze for p-aminohippuric acid: the substance is not more than 102 per cent.

flask

PERCOMORPH LIVER OIL.—A mixture containing the fixed oils obtained from the fresh livers of the percomorph fishes, containing not more than 50 per cent of other fish liver oil. It is biologically assayed and has a potency of not less than 60,000 units of vitamin A (U S P) per gram and of not less than 8,500 units of vitamin D (U S P) per gram.

Percomorph liver oil, 50%, in fish liver oil, is a yellow to brownish yellow, oily liquid. It has a slightly fishy but not rancid odor and a fishy taste. It is slightly soluble in alcohol, but is soluble in ether, chloroform, benzene, carbon disulfide and ethyl acetate. The specific gravity is from 0.922 to 0.930 at 25° C. The refractive index is from 1.480 to 1.485 at 20° C.

A solution of one drop of the oil in 1 cc. of chloroform, when shaken with one drop of sulfuric acid, acquires a blue color, changing to violet, dark green, and finally brown. Treat 5 cc. of oil with 5 cc. of benzene and centrifuge for 25 minutes at 25° C., no precipitate forms and a clear solution remains.

Fill a tall, cylindric, standard oil sample bottle of about 120 cc. capacity with percomorph liver oil, 50% in fish liver oil, at a temperature between 23 and 28° C., stopper, and immerse the bottle in a mixture of ice and distilled water for five hours; the oil remains fluid and forms no deposit.

Dissolve 2 Gm. of percomorph liver oil, 50%, in fish liver oil, in 20 cc. of a mixture of equal volumes of alcohol and ether, which previously has been neutralized with tenth normal sodium hydroxide, using 5 drops of phenolphthalein T.S. as indicator, and titrate with tenth normal sodium hydroxide to the production of a pink color which persists for fifteen seconds not more than 1 cc. of tenth normal sodium hydroxide is required (free acid). The amount of unsaponifiable matter as determined by the method of U S P XIII, p. 648, is not less than 3.5 per cent nor more than 7 per cent; it is semisolid in appearance.

PHENARSONE SULFOXYLATE.— $C_7H_8AsNNa_2O_6S$
—M. W. 355.11—Sodium 3-amino-4-hydroxyphenylarsonate-N-methanesulfonylate.

Phenarsone sulfoxylate occurs as a white, odorless, amorphous powder. It is soluble in water, dilute acids, alkalis and alkali carbonates, slightly soluble in methyl alcohol and insoluble in ether and alcohol. The pH of a 5 per cent solution is from 7.0 to 7.4.

Add 0.2 Gm. of sodium hydroxide to about 0.1 Gm. of phenarsone sulfoxylate dissolved in 5 cc. of water and warm at 50-60° C. for five minutes; a yellow solution is produced. Add normal hydrochloric acid dropwise to the solution; a lemon yellow gelatinous precipitate forms soluble in excess hydrochloric acid. Add 1 cc. of iodine solution and 2 cc. of chloroform to 10 cc. of a 1 per cent solution of phenarsone sulfoxylate, shake the test tube and contents and then allow the liquids to separate; no color appears in either of the liquid layers. Repeat the test, first adding 0.25 Gm. of sodium bicarbonate; no color appears in the chloroform layer, but the aqueous layer is colored light brown. Add 2 cc. of diluted nitric acid and 1 cc. of silver nitrate T.S. to 5 cc. of a 1 per cent solution of phenarsone sulfoxylate; a black precipitate forms. Heat to boiling and cool; the mixture rapidly changes to a yellow-brown solution.

containing a white precipitate. Decant the solution; the precipitate is soluble in excess strong ammonia solution. Add 3 drops of alkaline mercuric potassium iodide T.S. to 5 cc. of a 1 per cent solution of phenarsonic sulfoxylate: a gray to black precipitate of metallic mercury is formed (distinction from acetarsone, tryparsamide and other pentavalent arsenicals).

Dissolve 0.1 Gm of phenarsonic sulfoxylate in 5 cc. of water, add 0.5 cc. of a 10 per cent sodium nitrite solution, cool in ice water and add 0.1 cc. of 10 per cent hydrochloric acid followed by 0.1 cc. of a solution containing 5 per cent beta-naphthol and 10 per cent sodium hydroxide solution: no red color is produced on standing (absence of 3-amino-4-hydroxyphenyl-arsonic acid).

Dissolve 0.5 Gm of phenarsonic sulfoxylate in 10 cc. of water, add 1 cc. of diluted ammonia solution and 1 cc. of magnesia mixture: no precipitate forms (absence of inorganic arsenate). Heat the solution to boiling: a white precipitate forms slowly.

Dry an accurately weighed 1 Gm. portion of phenarsonic sulfoxylate,

cc. of water. Continue the digestion on the steam bath for 30 minutes, cool, allow to stand 30 minutes and collect the precipitated silver on a sintered glass filter (or Gooch crucible). Wash with water until the filtrate is free from silver. Dry the precipitate at 100° C. for 15 minutes and finally ignite at 650° C. for 15 minutes: the weight of silver sulfate formed is equivalent to a sulfur content of not less than 6.5 per cent nor more than 7.5 per cent.

Transfer about 0.5 Gm. of phenarsonic sulfoxylate, accurately weighed,

to a 250 cc. wide mouthed Erlenmeyer flask, add 10 cc. of water to dissolve the sample taken and then add 15 cc. of 30 per cent hydrogen peroxide. Mix and add 10 cc. of sulfuric acid slowly down the side of the flask, shaking the mixture after each addition. Place a short stemmed funnel in the top of the flask and heat at medium temperature until the reaction subsides. Remove the funnel and heat for twenty minutes at a temperature such as to produce sulfur trioxide fumes freely. (If at the

water and boil

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precipitate forms. Digest the mixture for one hour on the steam bath and

filter while hot, collecting the precipitated barium sulfate on a suitable

tared, previously ignited, Gooch crucible. Wash the precipitate with hot

water until chlorides are absent from the washings. Dry the crucible and

contents at 100° C. for 15 minutes and finally ignite at 650° C. for

15 minutes: the weight of barium sulfate formed is equivalent to a

sulfur content of not less than 6.5 per cent nor more than 7.5 per cent.

Transfer about 0.5 Gm. of phenarsonic sulfoxylate, accurately weighed,

to a 250 cc. wide mouthed Erlenmeyer flask, add 10 cc. of water to

dissolve the sample taken and then add 15 cc. of 30 per cent hydrogen

peroxide. Mix and add 10 cc. of sulfuric acid slowly down the side of the

flask, shaking the mixture after each addition. Place a short stemmed

funnel in the top of the flask and heat at medium temperature until the

reaction subsides. Remove the funnel and heat for twenty minutes at a

temperature such as to produce sulfur trioxide fumes freely. (If at the

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heat as before)

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20 cc of distilled water, add from 3 to 5 drops of a methyl orange solution (3 cc of methyl orange TS diluted to 100 cc with water) and titrate while hot with tenth normal potassium bromate until the solution becomes colorless. Near the end point the potassium bromate should be added dropwise. Each 1 cc of tenth normal potassium bromate is equivalent to 0.003746 Gm. of arsenic; the amount of arsenic found is not less than 17.0 per cent nor more than 18.5 per cent.

PHENOLTETRACHLOROPHTHALEIN.— $C_{20}H_8Cl_4$
 O_4 —M. W. 454.09

Phenoltetrachlorophthalein is a cream white powder, odorless, stable in the air. It is practically insoluble in water, very soluble in acetone, soluble in alcohol, ether and glacial acetic acid, and slightly soluble in chloroform, benzene and carbon disulfide. It dissolves in solutions of the alkalis and carbonates to form solutions which are deep purple when concentrated, but which change to violet red on dilution, and in very dilute solutions assume a bluish tint (*distinction from phenolphthalein*).

Phenoltetrachlorophthalein does not melt when heated to 300° C. It does not respond to the U. S. P. test for heavy metals as described under phenolphthalein.

Dry about 1 Gm. of phenoltetrachlorophthalein, accurately weighed, to constant weight at 115° C.; the loss is not more than 0.5 per cent. To about 5 Gm. of the substance accurately weighed, add 25 cc. of normal sodium hydroxide solution, boil for 5 minutes, cool, add 25 cc. of warm water, and allow to stand overnight. The solution is instant-ly tetra-colored.

PHENTETIOTHALEIN SODIUM— $C_{22}H_8I_4Na_2O_4$ —
 M. W. 889.96—Phenoltetraiodophthalein Sodium

Phentetiothalein sodium occurs as bronze purple, odorless, slightly hygroscopic granules. It is soluble in water and alcohol.

to a flat type weighing bottle and dry in a vacuum at 80° C. to constant weight, accurately weighed, of found is not less than 56 calculated to the dry basis.

8.5 per cent. Dissolve 10 mg. of phenylephrine hydrochloride in 1 cc. of water and add 1 cc. of cupric sulfate T.S. followed by 1 cc. of 20 per cent sodium hydroxide solution; a reddish purple color forms that is not extracted by ether. Dissolve 10 mg. of phenylephrine hydrochloride in 1 cc. of water and add 1 drop of ferric chloride T.S. a permanent amethyst purple color develops. Dissolve 20 mg. of phenylephrine hydrochloride in 3 cc. of alcoholic potassium hydroxide T.S., add 3 drops of chloroform and boil; there is no odor of carbilamine (*absence of primary amines*). Dissolve 50 mg. of phenylephrine hydrochloride in 30-40 cc. of distilled water, add 1 cc. of diluted hydrochloric acid in 1 cc. of barium chloride T.S.; no turbidity should result (*absence of sulfate*). Dissolve 0.2 Gm. of phenylephrine hydrochloride in 10 cc. of distilled water; the solution yields a negative test for heavy metals when tested according to the U. S. P. method (see U. S. P. XIII, p. 657). To 1 cc. of a solution containing 0.2 Gm. of phenylephrine hydrochloride add 2 drops of a freshly prepared 1 per cent sodium nitroprusside solution, then 1 cc. of sodium hydroxide T.S. followed by 0.6 cc. (10 drops) of glacial acetic acid; the final solution should not be a deeper yellow than the same reagents, without the phenylephrine hydrochloride (*absence of corresponding ketone*).

Heat about 0.2 Gm. of phenylephrine hydrochloride, accurately weighed, for twenty-four hours, in an oven at 100° C. the loss is not more than 1 per cent.

Transfer about 0.5 Gm. of phenylephrine hydrochloride, accurately weighed, to a platinum dish; ignite until constant weight is attained. the ash is less than 0.2 per cent.

Dissolve about 0.2 Gm. of phenylephrine hydrochloride, accurately weighed, in 200 cc. of water, heat to boiling, add 4 cc. of diluted nitric acid, followed by silver nitrate T.S. in slight excess, allow the container and mixture to stand for six hours, transfer to a Gooch crucible, wash well with diluted nitric acid (100 cc), dry at 100° C. cool or calculate from the silver chloride per cent not more than 17.70 per cent by the micro-Bohm method.

ONE PER CENT SOLUTION: Transfer

absolute

boiling

weight:

1.05 per

142° C.

Dissolve the residue in 3 cc. of water, add 10 drops of diluted ammonia solution, rub the glass container with a glass rod, filter the precipitate, wash with cold water on a porous plate the melting point of the phenylephrine base is 169-171° C.

PHENYLEPHRINE HYDROCHLORIDE ¼ PER CENT SOLUTION: Follow the assay procedure described for the 1 per cent solution except use a 25 cc. sample.

PHENYLMERCURIC BORATE TINCTURE 1:500.

per cent, alcohol 43.2 per g phenylmercuric borate 2 per cent, with 10 per phosphate.

the melting point of the phenylmercuric chloride is between 248° and 255° C. Evaporate 5 cc. of phenylmercuric borate tincture 1 500 on a water bath, cool, add 2 cc of methyl alcohol, ignite the solution the flame is green. To 2 cc of phenylmercuric borate tincture 1 500 add 2 cc. of water and 1 cc of silver nitrate TS a yellow precipitate forms, soluble in nitric acid.

To 2 cc. of phenylmercuric borate tincture 1 500 add 2 cc of water followed by 2 cc of potassium iodide TS, added a drop at a time a white precipitate forms in the solution that at no time shows traces of orange.

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solution

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PHENYLMERCURIC PICRATE TINCTURE 1:200 WITH PICRIC ACID.—A tincture consisting of acetone 10 per cent, alcohol 50 per cent and water 38.3 per cent, containing phenylmercuric picrate ($C_{12}H_7HgN_3O_7$ —M W 505.82) 0.5 per cent with picric acid (trinitrophenol) 1.2 per cent.

Phenylmercuric picrate tincture 1 200 with picric acid is a strongly yellow colored solution which possesses the odor of acetone and alcohol and a pH value of about 2.0. Its specific gravity is between 0.898 and 0.901 at 25° C.

To 2 cc. of phenylmercuric picrate tincture 1 200 add 2 cc of water and 2 drops of 1 per cent sodium chloride solution a white precipitate, which is soluble in sodium hydroxide and may be reprecipitated by the addition of nitric acid, is formed. To 10 cc of phenylmercuric picrate tincture 1 200 add 2 cc of saturated sodium chloride solution a precipitate forms. Filter, wash the precipitate with cold water, and dry it on a porous plate. The melting point of the phenylmercuric chloride is between 248° and 255° C.

To 5 cc of phenylmercuric picrate tincture 1 200 add 5 cc of water and 2 cc. of diluted nitric acid, extract the solution with three 10 cc portions of ether, combine the ether extracts, filter through a cotton pledget and evaporate the ether. The picric acid obtained melts (Caution!) from 120° to 123° C.

To 2 cc of phenylmercuric picrate tincture 1 200 add 2 cc of water and 2 drops of 1 per cent sodium chloride solution a white precipitate, which is soluble in sodium hydroxide and may be reprecipitated by the addition of nitric acid, is formed. To 10 cc of phenylmercuric picrate tincture 1 200 add 2 cc of saturated sodium chloride solution a precipitate forms. Filter, wash the precipitate with cold water, and dry it on a porous plate. The melting point of the phenylmercuric chloride is between 248° and 255° C.

To 5 cc of phenylmercuric picrate tincture 1 200 add 5 cc of water and 2 cc. of diluted nitric acid, extract the solution with three 10 cc portions of ether, combine the ether extracts, filter through a cotton pledget and evaporate the ether. The picric acid obtained melts (Caution!) from 120° to 123° C.

Should not appear (nitrate)
The mercury content of phenylmercuric picrate tincture 1 200 can be determined by a suitable electrolytic method. The mercury content is equivalent to not less than 0.26 per cent nor more than 0.28 per cent calculated as phenylmercuric ion. The phenylmercuric ion content also may be determined, as directed under phenylmercuric borate tincture 1 500, after removal by ether extraction of the picric acid from a portion of the tincture acidified with nitric acid.

Caution: Phenylmercuric picrate tincture 1:200 with picric acid is more subject to decomposition on aging than certain other phenylmercuric salts.

PHENYLPROPANOLAMINE HYDROCHLORIDE.
— $C_9H_{11}ClNO$.—M. W. 187.67.—*d*, 1-1-Phenyl-2-aminopropanol hydrochloride.

melts at 190-194° C.

Dissolve about 0.5 Gm. of phenylpropanolamine hydrochloride in 25 cc. of water and add 5 cc. of a saturated solution of sodium carbonate. Cool in an ice bath and collect the resultant needle-shaped crystals on a filter paper, wash and dry at 80° C.; the melting point of the α -hydroxy- β -amino-propylbenzene is 101-101.5° C.

Dissolve 0.05 Gm. of phenylpropanolamine hydrochloride in 100 cc. of water; separate portions of 2 cc. yield a yellow color with 5 drops of ferric chloride T.S. (distinction from *Cobefrin* and *epinephrine*); no precipitate with mercuric potassium iodide T.S. (distinction from *amphetamine*). To about 0.1 Gm. of phenylpropanolamine hydrochloride in 5 cc. of water, add 1 cc. of diluted hydrochloric acid and 1 cc. of barium chloride T.S.; no turbidity develops (*sulfate*).

Dry about 0.3 Gm. of phenylpropanolamine hydrochloride, accurately weighed, to constant weight at 100° C.; the loss in weight does not exceed 1 per cent. Incinerate about 0.3 Gm. of phenylpropanolamine hydrochloride, accurately weighed; the residue does not exceed 0.3 per

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according
ed. 6, page
to not less
the dried substance.

PHENYLPROPYLMETHYLAMINE. — $C_{10}H_{15}N$. —
M. W. 149.23 — *d*, 1-Methylamino-2-phenylpropane.

Phenylpropylmethylamine occurs as a colorless to pale yellow liquid at 25° C., with 98 per cent of

apor pressure of less than 25 and a refractive index of 1.525 (1.2 Gm. per 100 cc.) at 25° C. Aqueous solutions of phenylpropylmethylamine diluted with 10 cc

in 10 cc. of dry benzene, filter over calcium chloride, filter and recrystallize the solid from dry benzene. Wash the crystals with dry ether, and finally air-dry the crystals by suction. The phenylpropylmethylamine hydrochloride melts at 144-148° C.

Transfer about 0.5 Gm. of phenylpropylmethylamine accurately weighed, to a tared, low constant weight bottle, add 0.5 cc. of 10 per cent nitric acid and more chloride is

present than appears with a control containing 0.4 cc. of one hundredth normal hydrochloric acid.

Add 1 drop of each of the following solutions to 10 cc. aliquots of the solution and back titrate the excess acid with tenth normal sodium hydroxide, using methyl red T.S. as the indicator. Each cc. of tenth normal sulfuric acid is equivalent to 0.0149 Gm. of phenolphthalein.

100 ml. water

PHTHALYLSULFATHIAZOLE. — $C_{17}H_{11}O_5N_3S_2$ — M. W. 403.42 — 2 (N phthalylsulfanilamido)thiazole

Phthalylsulfanilamide
white
slowly
very
water
dilute
Ph
melts
bath
sample tube

Place about 0.25 Gm. of phthalylsulfathiazole in a test tube and add 3 cc. of 10 per cent sodium bicarbonate solution. The substance dissolves on warming and carbon dioxide is evolved (distinction from sulfanilamide, sulfathiazole, sulfapyridine, sulfaguanidine and sulfadiazine).

Add 10 cc. of concentrated hydrochloric acid to about 0.3 Gm. of phthalylsulfathiazole contained in a small beaker, cover with a watch glass and heat on a steam bath until the solid has nearly all dissolved. Cool the solution, transfer to a separatory funnel and extract with two 25 cc. portions of ether, combine the extracts and evaporate to dryness. The melting point of the residue is not less than 195° C.

Digest
at room
add two
sodium h
is require
add 1 cc
allow to
turbidity
cc. of fit

filtrate add 1 cc. of diluted hydrochloric acid and 1 cc. of barium chloride T.S., mix well and allow to stand for ten minutes. The turbidity does not exceed that produced in a control test made with 0.2 cc. of fiftieth normal sulfuric acid.

Dissolve 0.3 Gm. of phthalylsulfathiazole in a mixture of 5 cc. of one-normal sodium hydroxide and 20 cc. of distilled water. The solution is clear and not more than pale yellow, add five drops of freshly

prepared 10 per cent sodium sulfide solution: the darkening produced does not exceed that developed in a control test to which has been added 0.01 mg. of lead.

Dry an accurately weighed sample of phthalylsulfathiazole at 100° C. for 24 hours: the loss in weight does not exceed 2.0 per cent.

Ignite about 1 Gm. of phthalylsulfathiazole, accurately weighed. Cool, add 5 cc. of 10 per cent sodium nitrate solution, the colored mass and wash to red-

of ether, discarding the ether extracts. Heat the aqueous solution on a water bath until all of the ether is driven off. Add 5 cc. of concentrated hydrochloric acid, cool to 15° C. and slowly titrate with one-tenth molar sodium nitrite, stirring vigorously, until a blue color is produced immediately when a glass rod dipped into the titrated solution is streaked on a smear of starch-iodide paste T.S. When the titration is complete, the end point is reproducible after the mixture has been allowed to stand for one minute. Each cc. of one-tenth molar sodium nitrite is equivalent to 0.04034 Gm. of phthalylsulfathiazole: the amount of phthalylsulfathiazole found corresponds to not less than 96 per cent nor more than 102 per cent.

PIPEROCAINE HYDROCHLORIDE. — $C_{16}H_{23}NO_2$
HCl — M. W. 297.82. — *d,l*-3-Benzoxo-1-(2-methylpiperidino)
propane hydrochloride.

Crystalline, odorless
slightly bitter taste
1 air. Piperocaine
soluble in alcohol
1 aqueous solution
active. Piperocaine
hydrochloride melts at from 112 to 115° C. Small carbonates and hydroxides precipitate the free base from aqueous solutions as a water-white to a light yellowish oil which does not solidify at ordinary temperatures.

Dissolve about 1 Gm. of piperocaine hydrochloride in 10 cc. of water; divide into 2 cc. portions. To one portion add 1 cc. of diluted sulfuric acid and 1 cc. of potassium permanganate T.S.: the color is discharged. To a second portion add 1 cc. of gold chloride T.S.: a yellow precipitate appears. To a third portion add 2 drops of diluted hydrochloric acid, 2 drops of a 10 per cent sodium nitrate solution and gradually

metals).

Dry about 0.5 Gm. of piperocaine hydrochloride, accurately weighed, over sulfuric acid in a desiccator for 48 hours: the loss in weight does not exceed 0.25 per cent. Ignite ab-
is not more than 0.2 per cent
beaker, add 100 cc. of water,
normal silver nitrate solution
ous stirring and allow to cool in a dark place. Collect the
silver chloride on a Gooch crucible, wash with 1 per cent nitric acid,
followed by alcohol and ether; finally dry to constant weight at 105° C.

the amount of hydrogen chloride calculated from the silver chloride found corresponds to not less than 12 per cent, nor more than 12.35 per cent calculated to the dried substance

Transfer about 0.25 Gm of piperocaine hydrochloride, accurately weighed, to a suitable Squibb separatory funnel, add 50 cc of water, followed by the addition of 5 cc of diluted ammonia solution, extract

amount of tenth normal hydrochloride acid consumed corresponds to not less than 86.5, nor more than 88.0 per cent 3-benzoxyl-1-(2-methyl-piperidino)propane

ta

a white, heavy powder, soluble

potassium sodium bismuthyl
ole of metallic bismuth forms
idue is yellow and alkaline to

bismuthyl tartrate to a test
diluted hydrochloric acid to
dd 0.5 cc of barium chloride
tes

bismuthyl tartrate to a test
diluted nitric acid to dissolve
c of silver nitrate T.S. no

precipitate appears

Transfer about 1 Gm., accurately weighed, to a glass stoppered cylinder, add 50 cc. of ether, stopper and shake the contents for five minutes; decant the supernatant liquid through filter paper and repeat, using 25 cc. and 15 cc. portions respectively of ether.

Boilings of ether, allow the solvent to evaporate, leaving residue to constant weight. Ignite about 10 cc. of the residue with 5 cc. diluted ammonia solution, 25 cc. water and dilute with 20 cc. boiling ammonia solution; collect the precipitate on an ashless filter paper, wash with dilute ammonia hydroxide (1 part of diluted ammonia solution to 5 parts of water), transfer the precipitate to a platinum crucible, and ignite to constant weight: the weight of calcium oxide corresponds to not less than 8.0 per cent nor more than 8.5 per cent calcium.

PROBARBITAL SODIUM.— $C_{10}H_{13}N_2NaO_3$.—M. W. 220.21.—The sodium salt of 5-ethyl-5-isopropyl barbituric acid.

To one portion add 1 cc. of strong ammonia solution. To the other portion add 5 cc. of silver nitrate T.S.: a white precipitate results, soluble in an excess of strong ammonia solution.

Dissolve about 0.5 Gm of probarbital sodium in 50 cc. of water, add 5 cc. of diluted nitric acid and filter through paper: separate portions of 10 cc. each of the filtrate yield no opalescence on the addition of 1 cc. of silver nitrate solution (*chloride*); no turbidity on the addition of 1 cc. of barium nitrate T.S. (*sulfate*). To about 0.2 Gm of probarbital sodium in 25 cc of water, add 1 cc of diluted hydrochloric acid and filter through paper: the filtrate yields no color or precipitate on saturation with hydrogen sulfide (*salts of heavy metals*). Add about 0.1 Gm of probarbital sodium to 1 cc of sulfuric acid: the solution is colorless (*readily carbonizable substances*).

Transfer about 1 Gm. of probarbital sodium accurately weighed, to a glass stoppered cylinder, add 50 cc. of ether, stopper and shake for ten minutes; decant the supernatant liquid through filter paper and repeat twice, utilizing the same filter paper; dry the residue in a tared beaker at 100° C. exceed 0.2 per cent.

Dry about 1 Gm. weight at 100° C.

0.5 Gm. of probarbital sodium, accurately weighed, to a suitable separatory funnel, add 50 cc of water, followed by addition of 10 cc. of diluted hydrochloric acid, extract with eight successive 25 cc portions of ether, evaporate the combined ether extracts to dryness in a stream of warm air and dry to constant weight at 100° C.: the amount of ethylisopropyl barbituric acid corresponds to not less than 88.5 per cent nor more than 90.5 per cent, calculated to the dried substance.

Promethestrol dipropionate occurs as a white, colorless crystalline powder melting between 113 and 116 C. It is freely soluble in benzene, ether and ethyl acetate slightly soluble in alcohol and practically insoluble in water.

Distinction from benzenestrol, diethylstilbestrol, ethinyl estradiol, hexestrol and mestibol
 Add 1 drop of ferric chloride T₄ to 2 cc of a saturated solution of promethestrol dipropionate in diluted alcohol. The color is no different than that obtained by adding ferric chloride T₅ to the solvent (distinction from benzenestrol, diethylstilbestrol, hexestrol and mestibol, which give a slight greenish yellow color when the reagent is added).

Dry about 1 Gm of promethestrol dipropionate accurately weighed, in a vacuum desiccator over phosphorus pentoxide at room temperature for 24 hours; the loss in weight does not exceed 0.5 per cent.

Char about 0.5 Gm of promethestrol dipropionate accurately weighed, over a low flame. Cool, then add 1 cc of sulfuric acid and continue ignition until no carbon remains; no more than 0.05 per cent of residue results.

Place about 0.25 Gm of promethestrol dipropionate accurately weighed, in a 125 cc Erlenmeyer flask containing 10 cc of 0.5 N alcoholic sodium hydroxide. Reflux gently for 2 hours; cool and titrate the excess base with 0.1 N sulfuric acid, using phenolphthalein T₅ as indicator. The saponification equivalent (obtained by dividing the mass of promethestrol dipropionate used in milligrams by the number of cc of 1 N sodium hydroxide consumed in the saponification) is not less than 200 nor more than 210.

Add about 75 cc of water and 2 cc of sulfuric acid to the samples used in determining the saponification number. Distill and collect about 30 cc of the distillate. Titrate a 10 cc portion (A) of the distillate with 0.01 N sodium hydroxide. Redistill the remaining 40 cc of distillate, collecting three 10 cc fractions (B, C, D). Titrate each fraction with 0.01 N sodium hydroxide. The Duclaux numbers 10B/A, 10C/A, and 10D/A are not less than 10 and 17.

dipropionate, peroxide and reflux 10 minutes. Transfer the combined filtrate and washings to a 100 cc volumetric flask and dilute with ether solution to the mark. The solution obtained when more than 101.5 mg of sample is used for analysis melts at 150 and 158 C. The sample is dissolved in benzoyl chloride for 10 minutes and diluted ammonia

drops of sodium sulfide T.S. no more turbidity develops than corresponds to 20 p.p.m. of lead (*U. S. P. XIII*)

Weigh, accurately, about 0.5 Gm. of propylthiouracil and transfer to a 400 cc. beaker containing 100 cc. of neutralized alcohol. Add 5 drops of phenolphthalein T.S. Slowly titrate with tenth normal sodium hydroxide, stirring constantly until complete solution is effected. Continue the titration to the first faint pink color. Each cc. of tenth normal sodium hydroxide solution is equivalent to 0.01702 Gm. of propylthiouracil; the propylthiouracil content is not less than 95 per cent nor more than 105 per cent.

PSYLLIUM HYDROPHILIC MUCILLOID WITH DEXTROSE

Psyllium hydrophilic mucilloid with dextrose is a white to cream colored, slightly granular powder, possessing little or no odor and a slightly acid taste. A uniform suspension is formed when 10 Gm. of the powder is stirred rapidly into 250 cc. of water. As the hydration and swelling of the mucilaginous portion progresses, the mixture assumes a soft gelatinous consistency.

Psyllium hydrophilic mucilloid with dextrose is a white to cream colored, slightly granular powder, possessing little or no odor and a slightly acid taste. A uniform suspension is formed when 10 Gm. of the powder is stirred rapidly into 250 cc. of water. As the hydration and swelling of the mucilaginous portion progresses, the mixture assumes a soft gelatinous consistency.

As the hydration and swelling of the mucilaginous portion progresses, the mixture assumes a soft gelatinous consistency. The mixture is used for the determination of the optical rotation of a portion of the solution in a 2 decimeter tube, using sodium light. Multiple the observed angular rotation by 21.7 to obtain the percentage of anhydrous dextrose present in the specimen. The amount of dextrose found is not less than 45 per cent nor more than 50 per cent.

Ask. Allow the mixture to stand for ten minutes and then determine the optical rotation of a portion of the solution in a 2 decimeter tube, using sodium light. Multiple the observed angular rotation by 21.7 to obtain the percentage of anhydrous dextrose present in the specimen. The amount of dextrose found is not less than 45 per cent nor more than 50 per cent.

PYRETHRUM OINTMENT—Pyrethrum ointment is an unctuous, yellowish green mass.

Pyrethrum ointment is an unctuous, yellowish green mass. It is used for the determination of the optical rotation of a portion of the solution in a 2 decimeter tube, using sodium light. Multiple the observed angular rotation by 21.7 to obtain the percentage of anhydrous dextrose present in the specimen. The amount of dextrose found is not less than 45 per cent nor more than 50 per cent.

even when it is dry. It is insoluble in water and most organic solvents.

Treat about 0.5 Gm. of quinine bismuth iodide with 15 cc. of 20 per cent potassium hydroxide solution, warm, add 50 cc. of water, filter off the insoluble material, wash with water, dry at 100° C., extract with five 10 cc. portions of benzene, evaporate the benzene and dry the residue at 100° C.: the residue melts at 171° C. and responds to tests for quinine. Ash the filter and undissolved precipitate in a quartz crucible: a yellow residue remains.

Treat about 0.1 Gm. of quinine bismuth iodide with about 1 cc. of nitric acid: the material blackens. Add 10 cc. of water and boil: violet colored vapors are given off.

Shake 30 mg. of quinine bismuth iodide with 4 cc. of water, filter through a pledget of cotton, add 1 cc. of chloroform and 0.3 cc. each of diluted hydrochloric acid and ferric chloride T.S.; shake and allow to stand five minutes: the chloroform does not acquire a purple tinge (iodides).

Shake 0.75 Gm. of quinine bismuth iodide with 4 cc. of potassium iodide T.S., filter, add 1 cc. of chloroform to the filtrate, shake and allow to stand five minutes: the chloroform does not acquire a purple tinge (iodine).

Transfer about 0.5 Gm. of quinine bismuth iodide, accurately weighed, to a wide mouth weighing bottle and dry in a vacuum over sulfuric acid to constant weight: it loses not more than 1 per cent in weight. Transfer about 0.5 Gm. of the original, accurately weighed, to a 600 cc. beaker, add nitric acid until the color changes to black, add 100 cc. of water and boil until clear and almost colorless, add an excess of strong ammonia solution and 20 cc. of ammonium carbonate T.S., allow to stand three hours, filter and wash the precipitate with water. Ash the filter paper containing add a few drops of nitric acid to constant weight, cool in oxide weighed is equivalent to than 20.1 per cent of bismuth original, accurately weighed, to a Carius tube containing silver nitrate, seal and heat for tube, transfer the contents to a large beaker and dilute to 500 cc.; allow to stand for 4 hours, filter through a Gooch crucible, wash with 1 per cent nitric acid, dry at 100° C., cool in a desiccator and weigh: the silver iodide is equivalent to not less than 48.75 per cent nor more than 53.50 per cent iodine.

RACEPHEDRINE.— $C_{10}H_{15}NO$.—M. W. 165.23—*d*, *l*-Ephedrine—*d*, *l*-1-Phenyl-2-methylaminopropanol-1.

Racephedrine is a colorless, crystalline substance. The melting point of the free base is 79° C. (microscope heating stage). It is readily soluble in water, alcohol and ether. Weigh out, accurately, 0.2 Gm. of racephedrine, transfer to a desiccator and dry over phosphorus pentoxide for fifteen hours at room temperature: the loss of moisture is not more than 0.5 per cent. Ignite 0.1 Gm. of racephedrine, accurately weighed, and previously dried to constant weight: no residue remains. Dissolve approximately 0.5 Gm. of racephedrine in 20 cc. of water: the aqueous solution does not show optical activity and does not give the U. S. P. chloride and sulfate tests.

For further identification tests, see the monograph for racephedrine hydrochloride.

. accurately weighed, and previ-
at room tempera-
titrate with tenth-
T. S. as indicator.
cc of tenth-normal
s racephedrine.

RACEPHEDRINE HYDROCHLORIDE.— $C_{10}H_{15}ClNO$.—M. W. 201.69.—*d*, *l*-1-Phenyl-2-methylaminopropanol-hydrochloride.

Raceph-
is a col
racephed-
The solu
20° C.,
alcohol

Weigh, accurately, 0.2 Gm of racephedrine hydrochloride and keep over phosphorus pentoxide in an Abderhalden drier at 80° C., exhausted to 2 mm of mercury for five hours the loss of moisture is not more than 2 per cent. Ignite 0.2 Gm of racephedrine hydrochloride, accurately weighed, and previously dried to constant weight, as described no residue remains. Dissolve approximately 0.5 Gm in 20 cc of water the aqueous solution of racephedrine hydrochloride does not show optical activity. The solution gives the U S P test for chlorides. On addition of T S, no turbidity appears. Diluted hydrochloric acid on of barium chloride T S

phedrine hydrochloride is formed. To approximately add 2 cc. of 20 per cent sodium hydroxide solution only drops are formed. Extract the milky turbid mixture twice with 25 cc of ether the (racephedrine) base crystallizes out on slow evaporation of the ether, after recrystallization from ether and drying at room temperature over phosphorus pentoxide in a slight vacuum, the racephedrine melts at 76° C.

Dissolve approximately 0.2 Gm of racephedrine in 8 cc of distilled water; add 1 drop of 2 per cent cupric sulfate solution and 1 cc of 20 per cent sodium hydroxide solution a purple color is developed which, on shaking with ether, is partially dissolved in the ether layer. Evaporate the ether layer a pinkish residue remains. Place a drop of a 5 per cent solution of racephedrine hydrochloride on a microscope slide and introduce a small solid particle of potassium oxalate at an edge of the drop a crystalline precipitate immediately appears. The form of the crystals allows the distinction between optically active and racemic forms of ephedrine hydrochloride. The former gives bundles of needles and prisms, the latter, thin plates.

Dissolve 0.2 Gm of racephedrine hydrochloride, accurately weighed, and previously dried over sulfuric acid for 3 hours, in 20 cc of distilled water, and transfer the solution to a continuous liquid liquid extractor. Add 3 cc of 1 normal sodium hydroxide and extract with sufficient peroxide free ether (35 cc) for 3 to 5 hours. Wash the extract twice with 10 cc of distilled water and extract the wash water twice with 10 cc portions of ether. Combine the ether extracts and extract the ether with 15 cc of tenth normal sulfuric acid. Wash the combined ether extracts twice with 10 cc of distilled water. Carefully evaporate to 20 cc the acidified water solution and back titrate the excess acid with tenth normal sodium hydroxide the anhydrous racephedrine is not more than 82.5 per cent nor less than 80.0 per cent of the weight of racephedrine hydrochloride. (One cc of tenth normal sulfuric acid is equivalent to 0.01651 Gm of anhydrous racephedrine.)

RACÉPHEDRINE SULFATE. — $C_{10}H_{17}NO_5S$ — M. W. 263.3 — *d,l*-1 Phenyl 2-methylaminopropanol sulfate

Racephedrine sulfate is a colorless, crystalline substance. The melting point is 247° C. (microscope heating stage). The solubility is fair in water and alcohol. Dissolve 0.5 Gm in 25 cc. of distilled water. The aqueous solution is neutral to litmus and does not show optical activity. The U S P test for chloride is also negative. Weigh out accurately

SCARLET RED SULFONATE.— $C_{22}H_{14}N_4Na_2O_7S_2$.—M. W. 556.49.—The sodium salt of azobenzenedisulfonic acid azobetanaphthol.

Scarlet red sulfonate is a dark, brownish-red, odorless powder. It is soluble in water; slightly soluble in ether, alcohol and acetone; almost insoluble in chloroform, benzene, fixed oils, fats and petroleum.

Add diluted hydrochloric acid to a concentrated, aqueous solution of scarlet red sulfonate; red floccules separate from the orange red solution. Add sodium hydroxide T.S. to a concentrated aqueous solution of the substance; a brownish-red precipitate forms. Treat the substance with concentrated sulfuric acid a green solution results which becomes blue on the addition of water, and on further dilution, brownish-red floccules separate. Dissolve about 0.1 Gm. of the substance in 5 cc. of glacial acetic acid, heat to boiling, add zinc dust and continue the boiling; the liquid becomes almost colorless.

SCILLAREN (SANDOZ).—A mixture of the natural glycosides (Component-A and Component-B), occurring in fresh squill *Urginea maritima*, in the proportions in which they exist in the fresh crude drug; namely, about 2 parts of A to 1 part of B. The completely dried preparation contains approximately 98 per cent of the active glycosides.

This glycosidic mixture occurs as a white or yellowish-white, odorless granular powder, possessing a very bitter taste. It is freely soluble in absolute ethyl alcohol, 1 in 5, and in methyl alcohol, 1 in 5, sparingly soluble in water, 1 in 3,000; and practically insoluble in chloroform and in ether. An aqueous solution is neutral toward litmus. An alcoholic solution of the preparation is levorotatory.

Dissolve about 0.001 Gm. of the glycosidic mixture in 0.1 cc. of methyl

a
s
t
o
l
a reflux condenser on a steam bath, after five minutes the aglucone, begins to crystallize, continue heating for thirty minutes, cool, collect the resultant aglucone on a filter, wash with water and dry at 105° C.

acetate and the aqueous ammonium sulfate layers into a suitable separatory funnel, shake vigorously and allow the two layers to separate completely, filter the ethyl acetate solution through paper by the aid of suction into a small flask and evaporate to dryness. The residue mixed with 20 cc. of acetic anhydride and 0.5 cc. of sulfuric acid gives a violet blue color changing to the blue characteristic of component-B.

Dissolve about 0.025 Gm. of the glycosidic mixture in 2 cc. of methyl alcohol, a clear colorless solution results, which remains clear on dilution with an equal volume of carbon dioxide-free water (aglucone). Add to the foregoing solution 1 cc. of a mixture of equal volumes of methyl alcohol and lead acetate T.S.: a slight yellow coloration and opalescence

results in ten minutes but no precipitate (*appreciable amounts of tannoid substances*). Dissolve about 0.025 Gm. in a mixture of 2 cc of methyl alcohol and 2 cc of water, add 0.5 cc of alkaline cupric tartrate TS and heat for ten seconds; no turbidity results (*free reducing sugars*).

Dissolve about 0.5 Gm. of the glycoside mixture accurately weighed in 25 cc of 75 per cent (by weight) ethyl alcohol; observe the angular rotation at 20° C; the specific rotatory power in alcohol $[\alpha]_{20/D}$ falls between 25 and 35.

Ignite about 0.1 Gm. of the glycoside mixture accurately weighed; the residue does not exceed 0.25 per cent. Dry about 0.2 Gm. accurately weighed, over sulfuric acid in a partially exhausted desiccator for 48 hours at 20° C; the loss in weight does not exceed 4 per cent. The glycoside mixture dried in a high vacuum at 78° C for 15 hours loses not more than 5 per cent of its weight.

Weigh out accurately about 0.2 Gm. of the glycoside mixture previously dried over sulfuric acid in a partial vacuum. Transfer the sample to a 250 cc Erlenmeyer flask, dissolve in 5 cc of water and add 20 cc of 5 per cent sulfuric acid; heat on a steam bath for six hours; cool and collect the separated crystalline and oily residues in a Gooch crucible and wash free from acid with water; dry for 24 hours at 60° C and weigh; the amount of aglucone found is not less than 48 per cent nor more than 55 per cent.

Component A of the glycoside mixture responds to the following tests for identity and purity.

It occurs as small colorless odorless crystals or crystalline powder with a very bitter taste. It is soluble in ethyl alcohol 1 in 350 in methyl alcohol 1 in 80 in a mixture of 4 parts by volume of ethyl alcohol and 1 part by volume of water 1 in 40 and practically insoluble in chloroform and ether. It dissolves in water with difficulty, possessing a neutral reaction toward litmus. The specific rotation in 75 per cent alcohol $[\alpha]_{20/D}$ falls between 72 and 78 determined on the undried material.

Dissolve about 0.001 Gm. of component A in 0.1 cc of methyl alcohol and add 3 cc of acetic anhydride and 0.1 cc of sulfuric acid; shake; a red color results, it disappears rapidly and changes to a persistent light green (*this color reaction is due to the aglucone, of glycoside component A*). Dissolve about 0.1 Gm. in 10 cc of methyl alcohol; add 10 cc of tenth normal sulfuric acid; heat the mixture under a reflux condenser on a steam bath for thirty minutes; collect the resultant aglucone on a filter paper, wash with water and dry at 105° C; its melting point is not definite, occurring at about 20° C. The material responds to the foregoing color reaction. The neutralized filtrate reduces alkaline cupric tartrate TS immediately.

Dissolve about 0.025 Gm. component A in 2 cc of a mixture of 4 parts of ethyl alcohol (by volume) and 1 part of carbon dioxide-free water; a clear colorless solution results, which remains clear on dilution with an equal volume of carbon dioxide-free water (*aglucone*). Add to the foregoing solution 0.1 cc. of lead acetate TS; no immediate coloration or precipitate results (*appreciable amounts of tannoid substances*). Dissolve about 0.025 Gm. in a mixture of 2 cc of methyl alcohol and 2 cc of water, add 0.5 cc. of alkaline cupric tartrate TS and heat to boiling; the blue color persists for some time (*free reducing sugars*). Dissolve about 0.5 Gm. of component A accurately weighed in 25 cc of 75 per cent (by weight) of ethyl alcohol; observe the angular rotation at 20° C; the specific rotatory power in alcohol $[\alpha]_{20/D}$ falls between 72 and 74.

Ash about 0.1 Gm. of component A accurately weighed; the residue does not exceed 0.1 per cent. Dry about 0.2 Gm. accurately weighed over sulfuric acid in a partially exhausted desiccator for 48 hours at 20° C; the loss in weight does not exceed 2.5 per cent.

Weigh out accurately about 0.2 Gm. of component A previously dried over sulfuric acid in a partial vacuum. Transfer the sample to a 250 cc Erlenmeyer flask, add 10 cc of methyl alcohol and 10 cc of tenth normal sulfuric acid; reflux on a steam bath for 15 minutes; disconnect the condenser and boil on a steam bath until reduced to about a 10 cc volume; cool and collect the crystals formed on a Gooch crucible.

an aqueous solution containing the equivalent of 4.5 Gm of anhydrous scopolamine hydrobromide in 100 cc at a temperature of 15 C. in a 10 decimeter tube). The melting point of scopolamine hydrobromide is 195 C.

The absence of decomposition products is demonstrated by comparing the action of scopolamine hydrobromide solution with that of a freshly prepared solution of scopolamine hydrobromide by Langer's frog method. In this method the frog heart is stopped by muscarine, or, better, by pilocarpine, and the beat is reestablished by the addition of scopolamine, which is antagonistic to both muscarine and pilocarpine.

SECONAL SODIUM (Lilly)— $C_{12}H_{17}N_2NaO_3$ —M. W. 260.27.—The monosodium salt of 5-allyl-5-(1-methylbutyl) barbituric acid.

The sodium salt of this barbiturate occurs as a white hygroscopic, odorless powder, possessing a bitter taste. It is very soluble in water,

and boil until the precipitate dissolves and no oily particles float on the surface of the liquid. Allow the solution to stand overnight at room temperature. Collect the resultant crystals of allyl (1-methylbutyl) barbituric acid on a porous plate and dry at room temperature. The crystals melt between 96° and 107° C. Dissolve 0.3 Gm of the barbiturate salt in 10 cc. of distilled water and divide the solution into two portions, to one portion add 1 cc. of mercuric bichloride TS. a white precipitate results, soluble in excess of diluted ammonia solution. to the other portion add 5 cc. of silver nitrate TS. a white precipitate results, soluble in excess of diluted ammonia solution. Transfer about 0.5 Gm of the bar

dried substance

Transfer an accurately weighed sample of about 10 mg to a micro Kjeldahl flask and digest with 2 cc. of sulfuric acid and 0.01 Gm of

selenium. Dilute the clear solution to 10 cc., make alkaline with 30 per cent sodium hydroxide, and distil the ammonia into 10 cc. of one hundredth normal acid, using methyl red T.S. as indicator: the nitrogen content is not more than 10.85 nor less than 10.70 per cent, calculated to the dried substance.

SHARK LIVER OIL.—The oil extracted from the livers of the shark, mainly of the variety *Hypoprion brevirostris* (lemon), but any or all of the following varieties may be included: *Odontaspis littoralis* (sand), *Isurus punctatus* (mackerel), *Triakis semifasciatus* (leopard), *Sphyrna zygaena* (hammerhead), *Carcharias obscurus* (dusky), *Ginglymostoma cirratum* (nurse), *Carcharias milberti* (white) and *Carcharias*

A solution of one drop of the oil in 1 cc. of chloroform, when shaken with one drop of sulfuric acid, acquires a light violet color, changing to purple and finally brown or blue. Transfer 5 cc. of oil to a centrifuge tube and add 5 cc of benzene; centrifuge for 25 minutes at 25° C.: no precipitate forms and a clear solution remains.

The iodine value as determined by the method of the U. S. P. XII, p. 647, on from 0.18 to 0.20 Gm of sample, accurately weighed, is not less than 125 nor more than 145.

SILVER NITRATE $\text{CH}_3\text{AgNO}_3 \cdot \text{H}_2\text{O}$ W. 3540

Silver is light. It is soluble in acetone and

Dissolve in nitric acid and shake thoroughly. Excess of acid addition of

Dissolve in parts of water wash with not exceed acid and the with constant on a Gooch a small quantity 120° C. the corresponds

Caution—Sil-

in insoluble in ether. add 1 cc of nitric acid, use in an

about 150 g paper, ash does of nitric a time chloride owed by eight at a found or cent.

SOBISMINOL MASS.—A complex organic bismuth product the chemical nature of which has not been fully established. It is obtained by the interaction of sodium bismuthate, trisopropanolamine and propylene glycol. It contains between 19.25 and 20.25 per cent of bismuth, 0.75 Gm of sobisminol mass represents 150 mg of bismuth.

—Sobisminol mass occurs as a red brown to chocolate-brown colored pasty mass, possessing an
 bitter taste, with a sweetish,
 alcohol and partially soluble
 made by dissolving 1 Gm
 to make a volume of 10 cc
 a glass electrode

Dissolve 1 Gm of sobisminol mass in 10 cc. of water and halve the solution, to one portion add 5 cc of 0.5 per cent sodium bicarbonate solution, to the other portion add 5 cc of 0.1 per cent hydrochloric acid neither solution yields a precipitate within 15 minutes

Dissolve 2 Gm of sobisminol mass in 100 cc of water, boil a 5 cc portion the solution remains clear and unchanged. To a separate portion of 1 cc add 10 cc of water and 1 cc. of 5 per cent sodium iodide solution the solution remains clear. To another 1 cc portion add 1 cc of diluted hydrochloric acid, 5 cc of water and 5 cc of hydrogen sulfide T.S. a black precipitate forms. To another 1 cc portion add 3 cc.

T.S. to the other part when compared with the control, not more than a trace of turbidity is apparent (sulfate)

Transfer about 5.0 Gm of sobisminol mass, accurately weighed, to a 100 cc. volumetric flask, add water to the mark and shake the contents thoroughly. Determine the nitrogen content of an accurately measured 10 cc portion according to the method described in *Methods of Analysis of the Association of Official Agricultural Chemists* ed. 6, p. 27, paragraph 25. In the procedure add 0.1 Gm. of anhydrous copper sulfate and continue the digestion for a period of two and one-half hours after the solution becomes clear. The amount of nitrogen is not less than 3.60 per cent no more than 4.40 per cent.

Dissolve about 0.6 Gm of sobisminol mass, accurately weighed, in 100 cc of water and rapidly add 8 cc of concentrated nitric acid. Add

PROPYLENE GLYCOL ($C_3H_8O_2$ —M. W. 76.09). The propylene glycol used in the preparation of sobisminol mass and sobisminol solution con-

forms to The National Formulary standards for this substance, which see. *Sodium Bismuthate* (NaBiO_3 —M. W. 290). The sodium bismuthate isminol solution contains

yellow-brown powder

of 5 cc. of hydrochloric solution results, of water frequently added to phenolphthalein; evaporate 25 cc. of the solution and weigh; the

water for ten minutes, and divide into 10 cc. 1 cc. of silver nitrate that produced in a test. To another portion necessary, and add the turbidity should not containing 0.05 mg. of

sulfate ion (sulfate).

Heat 0.5 Gm. of sodium bismuthate with 3 cc. of sulfuric acid until fumes of sulfur trioxide appear, then complete the test for arsenic according to the method described in the U. S. P. XIII, p. 618; the arsenic content should not exceed 2 parts per million.

Dissolve about 0.25 Gm. of sodium bismuthate, accurately weighed, in 8 cc. of nitric acid, dilute with 100 cc. of water, and continue the assay for bismuth as directed in the last paragraph under sobisminol mass; the amount of bismuth found corresponds to not less than 66.3 per cent nor more than 72.5 per cent.

Transfer about 0.7 Gm. of sodium bismuthate, accurately weighed, to a flask and add 25 cc. of ferrous sulfate T.S., stopper the flask, allow it to stand one-half hour with frequent shaking, and titrate the excess ferrous sulfate with tenth normal potassium permanganate solution; the sodium bismuthate should not be less than 80 per cent NaBiO_3 . (The ferrous sulfate T.S. must be freshly prepared and standardized by a control titration).

TRISOPROPANOLAMINE ($\text{C}_9\text{H}_{21}\text{NO}_3$ —M. W. 191.27): The triisopropanolamine, $\text{N}(\text{C}_3\text{H}_7\text{OH})_3$, used in the preparation of sobisminol mass and sobisminol solution responds to the following tests for identity and purity:

Triisopropanolamine occurs as a colorless to pale yellow colored, pasty semicrystalline mass, possessing a slight characteristic odor and a bitter taste. It melts to a clear liquid at a temperature of not less than 46 C. Triisopropanolamine is readily soluble in acetone, alcohol, ether, chloroform and water.

Dissolve 1 Gm. of triisopropanolamine in 10 cc. of water: the solution is alkaline to litmus and only very slightly turbid. Dissolve 1 Gm. of triisopropanolamine in 20 cc. of water and divide the solution into two portions. To one portion add 0.5 cc. normal hydrochloric acid, filter, if necessary, and add to the clear filtrate 1 cc. of barium chloride T.S.; not more than a faint turbidity develops in five minutes (sulfate). To the other portion add 0.5 cc. of nitric acid and 1 cc. of silver nitrate T.S.; not more than a faint turbidity is produced (chloride).

The arsenic content of triisopropanolamine is not more than 2 p.p.m.; heavy metals are absent (U. S. P. XIII, p. 657). Ignite 5 Gm. of triisopropanolamine; the weight of the ash does not exceed 0.05 per cent.

Transfer about 5 Gm. of triisopropanolamine to a 100 cc. volumetric flask and assay for nitrogen as directed under sobisminol mass; the amount of nitrogen found is not less than 7.1 per cent nor more than 7.6 per cent. Dissolve about 1 Gm. triisopropanolamine, accurately weighed, in 50 cc. of distilled water and titrate with half-normal hydrochloric acid, each cc. of which is equivalent to 0.0955 Gm. of triisopropanolamine, using methyl red T.S. as the indicator; the triisopropanolamine content should be not less than 98.5 per cent nor more than 101.5 per cent.

SODIUM DEHYDROCHOLATE. — $C_{24}H_{33}NaO_5$ — M. W. 424.5.

Sodium Dehydrocholate occurs as a fine, colorless crystalline powder with a very bitter taste, soluble in water and alcohol. An aqueous solution is alkaline to litmus.

Dissolve about 1 Gm of sodium dehydrocholate in 200 cc of water, add an excess of hydrochloric acid, collect the resultant dehydrocholic acid on a filter, wash, and recrystallize from 80 per cent acetic acid, it melts at 233-238° C.

Dissolve about 0.5 Gm of sodium dehydrocholate in 100 cc of water, acidify with hydrochloric acid and filter. Separate portions of 10 cc. each of the filtrate yield no turbidity with 1 cc of barium chloride T.S. (sulfate), no color or precipitate on saturation with hydrogen sulfide (salts of heavy metals).

Dry about 1 Gm of sodium dehydrocholate accurately weighed, to constant weight at 100 C. The loss in weight does not exceed 7 per cent. Weigh accurately about 1 Gm in a tared platinum crucible, add 2 cc. of sulfuric acid, gently heat while fumes of sulfur trioxide are evolved, repeat, using two 1 cc portions of sulfuric acid, ignite, cool and weigh as sodium sulfate. The percentage of sodium corresponds to not less than 53 per cent, nor more than 56 per cent, when calculated to the dried substance.

SODIUM FOLATE.—Sodium pteroylglutamate—Sodium

... .. **SODIUM SOLUTION:** solut-
... .. ted to
... .. 1 Gm,

calcium hydroxide 0.14 Gm., inert salts 0.05 Gm. It contains not less than 3.85 per cent of available chlorine.

Sodium hypochlorite solution is prepared by decomposing chlorinated lime suspended in water with sodium carbonate.

Sodium hypochlorite solution has the properties of Solution of Chlorinated Soda U. S. P. X but contains no carbonate. When exposed to air, a pellicle forms on its surface owing to the formation of calcium carbonate.

To about 5 Gm of sodium hypochlorite solution, accurately weighed, slowly add 10 cc

residual acidity with tenth-normal sodium hydroxide: the alkalinity found corresponds to not more than 0.14 Gm. of calcium hydroxide per 100 Gm. of sodium hypochloride solution.

Mix in a flask about 5 cc. of sodium hypochloride solution, accurately weighed, with 50 cc. of distilled water; add 1 Gm. of potassium iodide and 5 cc. of acetic acid and titrate with tenth-normal sodium thiosulfate, starch test solution being used as indicator: it shows not less than 3.85 per cent of available chlorine. Each used corresponds to 0.003546 Gm should be made for a decrease in per cent per year, calculated from bottle

SODIUM IODOMETHAMATE.— $C_8H_3I_2NNa_2O$.—M. W. 428.95.—Disodium *N*-methyl-3,5-diiodo-4-pyridone-2,6-dicarboxylate.

Sodium iodomethamate occurs as a white, crystalline, odorless powder; and

. ater,
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. about
174 C., with decomposition. Heat the remainder of the sodium acid at its decomposition temperature (about 175 to 180 C.) until no further

calculated to the dried substance.

SODIUM PAMAMETHAMATE.— $C_8H_3I_2NNa_2O$.—M. W. 159.12.—

Sodium *p*-aminoben crystalline powder, pc slightly soluble in chloroform, and practically alkaline to litmus paper.

. in 45 cc. of water, and add flocculent, crystalline precipitate. Filter by suction test described later. Wash the

precipitate twice with small portions of cold water, recrystallize from alcohol, filter and dry at $110^{\circ}\text{C}.$, the *p*-aminobenzoic acid so obtained melts between 186° and 189°C .

Dry about 2 Gm of sodium *p*-aminobenzoate, accurately weighed, for three hours at 110°C the loss in weight does not exceed 7.5 per cent.

Dissolve 50 mg. of sodium *p*-aminobenzoate in 5 cc of water, add, in order, 0.5 cc of diluted hydrochloric acid, 0.5 cc of tenth molar sodium nitrite and 10 cc of ammonia water containing 0.2 Gm of *g*-naphthol a red color develops.

Place 50 mg of sodium *p*-aminobenzoate in a test tube containing 2 cc of water and add in order 0.5 cc of potassium iodide T.S., 0.4 cc of diluted hydrochloric acid and 0.5 cc of sodium hypochlorite T.S. a heavy brown precipitate forms (difference from *p*-aminohippuric acid).

An aqueous solution (1 in 10) responds to the tests for sodium (U.S.P. XIII, p. 663).

Transfer about 1 Gm of sodium *p*-aminobenzoate, dried and accurately weighed, to a 25 cc Erlenmeyer flask containing 5 cc of water and add 2 drops of phenolphthalein T.S. no more than 0.5 cc of fiftieth normal sulfuric acid is required to discharge any pink color which may develop.

Transfer about 0.3 Gm of sodium *p*-aminobenzoate, dried and accurately weighed, to a platinum crucible and ash to a white residue. Cool, add carefully a few drops of sulfuric acid and ignite to constant weight the weight of the sulfated ash calculated as sodium sulfate is not less than 44.1 nor more than 44.5 per cent.

A 0.2 Gm sample of sodium *p*-aminobenzoate shows no more chloride than corresponds to 0.15 cc of fiftieth normal hydrochloric acid (U.S.P. XIII, p. 709). A 0.3 Gm sample of sodium *p*-aminobenzoate shows no more sulfate than corresponds to 0.1 cc of fiftieth normal sulfuric acid (U.S.P. XIII, p. 709). The heavy metals limit (U.S.P. XIII, p. 657) of 25 cc of the filtrate obtained previously in the melting point procedure is 20 ppm.

Transfer about 0.3 Gm. of sodium *p*-aminobenzoate, accurately weighed, to a 250 cc beaker. Add 5 cc of hydrochloric acid and 50 cc of water. Mix to obtain complete solution, cool to 15°C , and add about 25 Gm of crushed ice. Slowly titrate with tenth molar sodium nitrite, previously standardized against sulfanilamide (U.S.P. XIII, p. 865), until a blue color is produced immediately when a glass rod dipped into the titrated solution is streaked on a smear of starch iodide paste T.S. When the titration is complete, the end point is reproducible after the mixture has been allowed to stand for one minute. Each cc of tenth molar sodium nitrite is equivalent to 0.01391 Gm of sodium *p*-aminobenzoate the sodium *p*-aminobenzoate content, calculated on the dry basis, is not less than 98 nor more than 101 per cent.

SODIUM PEROXIDE— Na_2O_2 —M. W. 77.99

Sodium peroxide occurs in the form of a white or yellowish, amorphous powder. It is soluble in water (caustic), with decomposition and evolution of heat, forming an alkaline solution and liberating oxygen. It dissolves in cold dilute acids, forming a solution of hydrogen peroxide. When heated, sodium peroxide becomes darker, but on cooling resumes its original color. It does not react with alcohol but it ignites ether on contact. A mixture with red phosphorus explodes under pressure on being struck. It is an extremely powerful oxidizing agent.

Sodium peroxide should not respond to tests for sulfates, chlorides, phosphates, nitrates and heavy metals. If 1 Gm or 1.5 Gm of sodium peroxide is weighed and gradually added with constant stirring to 950 cc of 1 per cent sulfuric acid and the solution made up to 1000 cc, the titration of 100 cc of this solution with tenth normal potassium permanganate will indicate the presence of not less than 90 per cent sodium peroxide.

Caution—Sodium peroxide yields spontaneously explosive mixtures with many organic substances and the dry material may react violently with moist air.

SODIUM RICINOLEATE SOLUTION.— $\text{C}_{18}\text{H}_{33}\text{O}_2\text{Na}$ —M. W. 320.45—A sterile, aqueous solution containing 2 Gm. of purified sodium ricinoleate per 100 cc.

Sodium ricinoleate solution, 2 per cent, occurs as a clear, odorless, pale yellow liquid. The pH is not less than 8.2 nor more than 8.5.

Transfer 50 cc. of sodium ricinoleate solution, 2 per cent, to a suitable separatory funnel, acidify with diluted sulfuric acid and extract with chloroform, using 25 cc., 20 cc., 20 cc., 15 cc and 10 cc. portions, respectively. Filter the combined chloroform extracts through a pledget of cotton into a tared beaker. Evaporate the chloroform to dryness on a steam bath, dry the residue at 100° C. for one hour, and weigh: the residue calculated to sodium ricinoleate should be not less than 0.018 Gm. and not more than 0.022 Gm. per cc.

SODIUM TETRADECYL SULFATE.— $C_{14}H_{29}NaO_4S$.
—M. W. 316.43.—Sodium-2-methyl-7-ethylundecyl sulfate-4.

Sodium tetradecyl sulfate occurs as a white, waxy, odorless solid. It is soluble in alcohol, ether and colorless. The pH

Add 3 drops of 5 per cent ortho-phenanthroline solution
Dissolve 1 Gm of sodium tetradecyl sulfate in 25 cc. of water

hydrogen sulfide T.S. and allow to stand ten minutes: no more color develops than corresponds to 20 p.p.m. of lead (U. S. P. XIII, p. 657).

Dry 2 Gm. of sodium tetradecyl sulfate, accurately weighed, in a vacuum desiccator for 48 hours: the loss in weight is not more than 10 per cent. Weigh, accurately, 1 Gm. of sodium tetradecyl sulfate into a tared platinum dish, add 2 cc. of sulfuric acid, and heat gently to avoid spattering until no more fumes of sulfur trioxide are evolved. Repeat this treatment twice, then ignite and weigh. The sulfated ash content is not less than 19 nor more than 25 per cent of the dry substance.

Weigh, accurately, about 0.3 Gm. of sodium tetradecyl sulfate into a suitable flask. Add 2 drops of bromocresol purple T.S., and neutralize with tenth normal hydrochloric acid. Add slowly, with shaking, 25 cc. of a five-hundredths normal sodium hydroxide solution. Shake well and allow to stand at room temperature. Add 25 cc. of distilled water and wash 4 times with distilled water.

purple T.S. Titrate the hot alcoholic solution with five-hundredths normal sodium hydroxide using bromocresol purple T.S. as the indicator. Each cc. of five-hundredths normal sodium hydroxide is equivalent to 0.0158 Gm. of sodium tetradecyl sulfate. The sodium tetradecyl sulfate found is not less than 85 per cent of the dry substance.

STARCH-DERIVATIVE DUSTING POWDER.—A biologically absorbable powder prepared from cornstarch by etherification with epichlorohydrin. The starch polymer chains are presumably cross-linked by 1,3-diether glycerine groups to the extent of not more than 2 per cent of the original starch weight. The starch derivative is mixed with magnesium oxide, 2 per cent, and small residual amounts of sodium sulfate and sodium chloride.

Starch Derivative dusting powder is an odorless, white powder. The pH of a 10 per cent suspension of starch-derivative dusting powder in distilled water is 10.4-10.8.

Determine the particle-size distribution of starch derivative dusting powder with Tyler screens of 60, 100 and 200 mesh: no more than 0.1 per cent of starch derivative dusting powder should be retained on the 60 mesh screen, no more than 3.0 per cent on the 100 mesh screen and, no more than 8.0 per cent on the 200 mesh screen.

Determine the amount of swelling of starch-derivative dusting powder in hot water as follows: Boil 100 cc. of a 10 per cent suspension of starch-derivative dusting powder in distilled water for 20 minutes. Pour the cooled suspension into a 100 cc graduated cylinder, add water to the 100 cc mark and allow the graduate to stand, undisturbed, for 24 hours:

the settled starch-derivative dusting powder should occupy a volume of not more than 60 cc

Dry about 2 Gm of starch-derivative dusting powder, accurately weighed, contained in a tared weighing dish of from 40 to 50 mm. diameter, to constant weight at 105° C (2 hours) the normal moisture content is 10 per cent

Char 1 Gm of starch-derivative dusting powder, accurately weighed, in a covered platinum crucible until most of the carbon is burned away (avoid igniting the sample) Remove the cover and ignite the residue to constant weight the ash does not exceed 3 per cent of the sample as received

Dissolve the ash obtained in the ignition of starch-derivative dusting powder in a few cc of diluted hydrochloric acid Transfer the solution to a beaker and make it up to 100 cc with distilled water Add 20 cc of ammonium phosphate, dibasic, T S then add strong ammonia solution dropwise, until the solution is neutral to litmus, and finally add 10 cc excess Allow the precipitate to settle 4 hours or overnight filter the mixture through ashless filter paper, and wash the precipitate with cold

overnight in the dark Filter the silver chloride onto a tared Gooch crucible, wash with dilute nitric acid (1:1000) until the washings are free of silver and then wash successively with small portions of water alcohol and ether Dry to constant weight at 100° C, and weigh Run a blank on the fusion mixture and make the appropriate corrections Each Gm of silver chloride is equivalent to 0.2473 Gm of chloride the chloride content does not exceed 0.2 per cent of the sample weight

STIBAMINE GLUCOSIDE C. H. C. M. S. M.

F W 1264

stibonate —

by the conc

in a slight

lute alcohol

assigned to stibamine glucoside is based upon the assumption of a trimer linked through the stibonic group

Stibamine glucoside occurs as an odorless, pale cream to light buff

colored, amorphous powder. It is soluble in water. The pH of a 6 per cent solution is from 8.5 to 9.0.

Heat 0.5 Gm. of stibamine glucoside dissolved in sodium carbonate solution: the vapors do not turn moist red litmus paper blue (*distinction from ethylstibamine which turns red litmus blue*).

Acidify the solution remaining after the assay for total antimony and saturate it with hydrogen sulfide: an orange colored precipitate is formed.

Dissolve 0.1 Gm. of stibamine glucoside in 5 cc. of water, add 5 cc. of 10 per cent sodium carbonate solution, and extract with 20 cc. of ether. Wash the ether extract with 10 cc. of water and extract with 5 cc. of

cc. of tenth-normal

and add two drops

cent naphthylethyl-

similarly treating

0.1 mg. of antimony.

Acidify the extracted sodium carbonate solution with diluted hydrochloric acid. Add two drops of sodium nitrite solution, and pour into a freshly prepared alkaline solution of "H" acid (1-amino-8-naphthol-3,6-disulfonic

reagents except the assay sample. Before beginning the titration with tenth-normal sodium thiosulfate, add about 150 cc. of water and 6 cc. of starch T.S. The blank should require no more than 0.4 cc. of tenth-normal sodium thiosulfate; the exact amount is deducted from the principal titration figure. Each cc. of tenth-normal sodium thiosulfate is equivalent to 6.09 mg. of antimony. The amount of antimony found is equivalent to not less than 24 per cent nor more than 27 per cent, calculated to the dried substance.

STILPALMITATE.— $C_{50}H_{80}O_4$ —M. W. 745.14.—Diethylstilbestrol dipalmitate.—The dipalmitic acid ester of diethylstilbestrol.

Stilpalmitate occurs as a white to yellowish odorless, waxy, crystalline powder. It is practically insoluble in water; slightly soluble in alcohol; sparingly soluble in fatty oils at room temperature, but dissolves

more freely on warming, and soluble in ether and chloroform. It melts between 81° and 83° C.

Dry about 0.25 Gm of stipalmitate over concentrated sulfuric acid in a vacuum desiccator for 24 hours: the loss in weight is not more than 0.1 per cent.

Transfer about 13.35 mg of stipalmitate, accurately weighed, to a 125 cc Erlenmeyer flask. Add 10 cc of alcohol and 3 drops of concentrated sulfuric acid. Hydrolyze in a boiling water bath under a reflux condenser for two hours. Transfer the solution quantitatively to a 100 cc volumetric flask and make up to volume with alcohol. To 5 cc of this hydrolyzed solution placed in a 100 cc. volumetric flask, add 5 cc of distilled water, 2 cc of diluted hydrochloric acid, 4 cc of molybdophosphotungstate TS (U S P) and 50 cc. of distilled water. Allow to stand for ten minutes, then add 10 cc of a 25 per cent aqueous solution of anhydrous sodium carbonate, dilute to exactly 100 cc, mix well and allow to stand for 45 minutes. Filter the solution through a dry filter, rejecting the first portion of the filtrate. Treat a 5 cc portion of diethylstilbestrol stanc. Reference standard in of reagents and in th a 5 cc portion of alc. Determine the optical

SULFAPYRAZINE.— $C_{10}H_{10}N_4O_2S$ —M W 250.27—p Amino-N-2 pyrazinylbenzenesulfonamide

Sulfapyrazine occurs as an odorless tasteless white or yellowish white, crystalline powder, which may darken on exposure to light. It is soluble in aqueous solutions of sodium, potassium and barium hydroxide,

fed)

To 0.1 Gm of sulfapyrazine add 0.5 cc of tenth normal sodium hydroxide and dilute to 10 cc with distilled water. Add five drops of cupric sulfate TS: a light pea green precipitate forms which becomes white on standing (distinction from sulfapyridine, which forms an apple green precipitate that turns olive green, from sulfadiazine, which forms an olive green precipitate changing to purple gray on standing, from sulfamerazine, which gives an olive green precipitate changing to dark gray on standing, from sulfathiazole, which forms a violet precipitate, from sulfaguanidine which forms a dark brown pre-

citrate; and from sulfanilamide, which forms no precipitate or a light blue one).

Digest 2.0 Gm. of sulfapyrazine with 100 cc. of distilled water at about 70° C. for five minutes; cool and filter. (1) To 25 cc. of filtrate add two drops of phenolphthalein T.S. and titrate with tenth-normal sodium hydroxide; not more than 0.1 cc. of sodium hydroxide is required to produce a pink color. (2) To another 25 cc. of the filtrate add 1 cc. of nitric acid and 1 cc. of silver nitrate T.S.; mix well and allow to stand five minutes protected from direct sunlight; the turbidity does not exceed that produced in a control test made with 0.1 cc. of fiftieth-normal hydrochloric acid. (3) To another 25 cc. of the filtrate add 1 cc. of dilute hydrochloric acid and 1 cc. of barium chloride T.S.; mix well and allow to stand ten minutes; the turbidity does not exceed that produced in a control test made with 0.2 cc. of fiftieth-normal sulfuric acid.

Dissolve 0.5 Gm. of sulfapyrazine in a mixture of 5 cc. of sodium hydroxide T.S. and 20 cc. of distilled water; the solution is clear and not more than pale yellow in color; add five drops of freshly prepared sodium sulfide T.S.; the darkening produced does not exceed that developed in a control test to which has been added 0.01 mg. of lead.

Dry an accurately weighed specimen of sulfapyrazine at 100° C. for 24 hours; the loss in weight does not exceed 0.2 per cent.

Ignite about 1 Gm. of sulfapyrazine, accurately weighed. Cool, add sufficient sulfuric acid to moisten the charred mass and ignite to constant weight; the ash is not more than 0.1 per cent.

Dissolve about 0.5 Gm. of sulfapyrazine in 10 cc. of distilled water and 10 cc. of hydrochloric acid contained in a 250 cc. beaker, dilute to 50 cc., cool to 15° C., and titrate with tenth-molar sodium nitrite. The endpoint is the first blue streak obtained immediately when a glass rod dipped into the solution is drawn across a smear of starch-iodide paste on white filter paper (or on a clear glass plate). The solution should retain this endpoint for 30 seconds. Each cc. of tenth-molar sodium nitrite corresponds to 0.02503 Gm. of anhydrous sulfapyrazine; the amount of sulfapyrazine found corresponds to not less than 99.0 per cent nor more than 101.0 per cent.

SULFAPYRAZINE SODIUM.— $C_{10}H_9N_4NaO_2S \cdot H_2O$ —M. W. 290.28.—The monohydrated sodium salt of 2-sulfanilamidopyrazine.

Sulfapyrazine sodium occurs as a white, odorless, bitter tasting powder, which darkens on exposure to light. It is freely soluble in water (1 Gm. in 3.33 cc. at 25° C.), very soluble in acetone, slightly soluble in alcohol, and insoluble in ether and chloroform. Aqueous solutions of sulfapyrazine

at 100° C. lose any precipitate formed under Sulfapyrazine-N. N. R.

Dissolve 0.5 Gm. of sulfapyrazine sodium in 25 cc. of distilled water; the solution is clear, not more than a pale yellow, and meets the requirements for heavy metals given under Sulfapyrazine-N. N. R.

Dry an accurately weighed portion of sulfapyrazine sodium at 110° C. for four hours; the loss in weight is not less than 6.1 per cent nor more than 6.4 per cent. Ash 0.2 Gm. of anhydrous sulfapyrazine sodium, accurately weighed, with the addition of 0.5 cc. of sulfuric acid, ignite until the carbon residue has been burned off, add 0.5 cc. of sulfuric acid, heat gently to drive off the excess acid, and ignite to constant weight; the weight of sodium sulfate formed is not less than 24.8 per cent nor more than 26.2 per cent.

Dissolve about 0.5 Gm. of anhydrous sulfapyrazine sodium, accurately weighed, in 10 cc. of distilled water and 20 cc. of hydrochloric acid contained in a 250 cc. beaker, dilute to 50 cc., cool to 15° C., and titrate with tenth-molar sodium nitrite. The endpoint is the first blue streak

obtained immediately when a glass rod dipped into the solution is drawn across a smear of starch iodide paste on white filter paper (or on a clear glass plate). The solution should retain this endpoint for 30 seconds. Each cc. of tenth molar sodium nitrite corresponds to 0.02723 Gm. of anhydrous sulfapyrazine sodium; the amount of sulfapyrazine sodium found corresponds to not less than 99.0 per cent nor more than 101.0 per cent.

methylglucamine

Transfer a portion of powdered tablets or of solution, equivalent to approximately 0.35 Gm. of theophylline methylglucamine to a separatory funnel. Add 25 cc. of water and 2 drops of methyl red T.S., and titrate to a faint red color with tenth normal hydrochloric acid. Each cc. of tenth normal hydrochloric acid is equivalent to 19.52 mg. of methylglucamine. The amount of methylglucamine found is not less than 95 per cent nor more than 105 per cent of the labeled amount of methylglucamine.

To the mixture that has been titrated in the separatory funnel, add 4 drops of tenth normal hydrochloric acid and extract with 4 portions of 25 cc., 20 cc., 15 cc., and 15 cc. of a mixture of three volumes of chloroform and one volume of isopropyl alcohol. Filter the extract through a small dry filter paper into a dried and tared evaporating dish. Wash the filter with a small amount of the extraction solvent and evaporate the combined extract and washings on a water bath. Dry the residue to constant weight at 100° C.; the weight of the residue, multiplied by 1.100, is equivalent to not less than 95 per cent nor more than 105 per cent.

Dissolve 1 Gm. of methylglucamine in 25 cc. of water; the heavy metals limit (U. S. P. XIII, p. 657) is 20 ppm.

The nitrogen content of methylglucamine when determined by the Dumas method, is not less than 7.0 per cent nor more than 7.2 per cent.

per cent, calculated to the dry substance

20
S
of
171
98

52 per cent Theophylline-U. S. P. It is considered to exist in a state of equilibrium

odorless powder with
decomposes between 190°
decomposed by acids.
tests for Theophylline in

powder responds to the

these tablets respond to
p. 566

Place 5 suppositories in a beaker containing 50 cc. of water and dissolve them by heating on a steam bath. Cool the beaker in an ice bath until the fatty material congeals. Filter the solution through glass wool into a 250 cc. volumetric flask. Transfer the glass wool and residue to the original beaker. Add 50 cc. of water, heat the beaker on a steam bath, and again cool it in an ice bath and filter the solution through glass wool into the volumetric flask. Repeat the operation once more. Dilute the combined filtrates to volume. Proceed as directed in the U.S.P. XIII, p. 566, under the Theophylline assay beginning with "Transfer an accurately measured aliquot of the filtrate . . ."

THIOUREA.— $\text{CH}_4\text{N}_2\text{S}$ —M. W. 76.12.

Thiourea is a white, crystalline, almost odorless solid. It is slightly soluble in cold alcohol and very slightly soluble in chloroform and ether. When 50 mg. is dissolved in 10 cc. of water to which 2 drops of ferric chloride T.S. have been added, the color is only slightly deepened (sulfocyanates). Warm 50 mg. of thiourea in a test tube until it melts, cool, add 10 cc. of water and 2 drops of ferric chloride solution; a blood red color results. Add 10 cc. of water and 4 cc. of diluted nitric acid to a mixture of 0.1 Gm. bismuth nitrate and 0.3 Gm. of thiourea, and warm; an orange colored solution results, which upon evaporation yields orange crystals. The melting point of thiourea ranges from 176° to 180° C.

Thonzylamine hydrochloride occurs as a white, crystalline powder having a faint odor. It melts between 173° and 176° C. It is very soluble in water, freely soluble in alcohol and chloroform, and practically insoluble in ether. The free base is obtained as an oil upon the addition of 5 per cent sodium hydroxide to an aqueous solution of thonzylamine hydrochloride. A 2 per cent aqueous solution of thonzylamine hydrochloride has a pH between 5.1 and 5.7.

Dissolve about 25 mg. of
Add a few drops of nitric acid
a white precipitate of silver
thonzylamine hydrochloride
obtained which turns red upon standing.

Add 3 drops of a saturated aqueous solution of Reinecke's salt to 2 cc. of a 2 per cent aqueous solution of thonzylamine hydrochloride; a pink precipitate is formed.

Dissolve about 0.1 Gm. of thonzylamine hydrochloride in 25 cc. of water and add the solution to 25 cc. of a saturated aqueous solution of picric acid containing 0.2 cc. of sulfuric acid. The yellow thonzylamine dipicrate obtained melts between 141° and 145° C.

dipicrate obtained melts between 141° and 145° C. Add

over a low flame. Cool, then add 1 cc of sulfuric acid and continue ignition until no carbon remains; the residue should not exceed 0.1 per cent.

Transfer 0.1 Gm. of thonzylamine hydrochloride, accurately weighed, to a 100 cc volumetric flask and dilute to the mark with alcohol. Mix thoroughly and transfer 10 cc of the solution to another 100 cc volumetric flask. Dilute to 100 cc with alcohol; mix well and transfer 10 cc of the solution to a third 100 cc volumetric flask and dilute to 100 cc. The final solution (0.001 per cent) exhibits an ultraviolet absorption maximum at 2440 Å ($E_{1\%}^{1\text{cm}} = 750 \pm 7$) with minor peaks at approximately 2780, 2835 and 3070 Å, and exhibits minimums at approximately 2680, 2800 and 2920 Å.

Transfer 0.1 Gm. of dry thonzylamine hydrochloride to a semimicro Kjeldahl flask and digest with 5 cc of sulfuric acid, 2 Gm of potassium sulfate, 0.2 Gm of copper sulfate and 1 cc of 30 per cent hydrogen

weighed to a separatory funnel. Add 50 cc of water, 8.0 cc of 10 per cent sodium hydroxide and extract the mixture with four 25 cc portions of ether. Collect the ether extracts in a separatory funnel and wash them successively with two 10 cc and one 5 cc portions of water. Combine the water extracts, saturate them with sodium chloride, extract them with

preparation of

thrombin (bovine)
water or isotonic
1 mg of protein
phosphorus pentoxide
e loss in weight
more than 5 mg
en at 50° C for

TRIMETHADIONE— $\text{C}_8\text{H}_9\text{NO}_3$ —M W 143.14—3,5,5-Trimethyloxazolidine 2,4 dione

Add 3 cc. of 25 per cent sodium hydroxide to 0.5 Gm. of trimethadione. Heat for thirty minutes on a boiling water bath. Carefully evaporate the solution to 0.5 cc. over a free flame, during the course of which a heavy precipitate forms. Cool and carefully treat the residue with hydrochloric acid until the resulting solution is acid to litmus. Add 1 drop of ferric chloride T.S. to 10 drops of the aforementioned solution: a deep yellow color develops.

Extract the acid solution obtained as described in the preceding paragraph with three 10 cc. portions of ether. Remove the ether, the residue and combine the solution to dryness on the water bath. The melting point of the residue is 101-102°.

Accurately weigh about 10 mg. of the product obtained as described in the previous paragraph. Transfer to a 150 cc. beaker, add 3 drops of alcohol to effect solution and follow with about 25 cc. of water. Add two drops of phenolphthalein T.S. and titrate with one-hundredth normal sodium hydroxide: the neutralization equivalent is within the limits 101-107.

Dry 0.5 Gm. of trimethadione over phosphorus pentoxide for 24 hours. Weigh about 0.1 Gm. of the residue and weigh it in about 5 cc. of alcohol and then add 25 cc. of water followed by 25 cc. of tenth-normal sodium hydroxide. Allow to stand for 15 minutes add 4 drops of hydrochloric acid and allow to stand for 15 minutes add 4 drops of sodium hydroxide.

Ash about 0.1 Gm. of the residue and weigh it in about 5 cc. of alcohol and then add 25 cc. of water followed by 25 cc. of tenth-normal sodium hydroxide. Allow to stand for 15 minutes add 4 drops of hydrochloric acid and allow to stand for 15 minutes add 4 drops of sodium hydroxide.

Weigh accurately 0.1 Gm. of the residue and weigh it in about 5 cc. of alcohol and then add 25 cc. of water followed by 25 cc. of tenth-normal sodium hydroxide. Allow to stand for 15 minutes add 4 drops of hydrochloric acid and allow to stand for 15 minutes add 4 drops of sodium hydroxide.

TRIMETHADIONE CAPSULES. Weigh sufficient powder from ten capsules to obtain about 0.1 Gm. of trimethadione. Transfer to a small beaker, add 5 cc. of alcohol and allow to stand for five minutes. Decant the alcohol through filter paper previously moistened with alcohol. Repeat the extraction with alcohol and the filtration twice more. Dilute the combined filtrates to four times their original volume with water. Add 20 cc. of tenth-normal sodium hydroxide to the solution and allow it to stand for five minutes, add two drops of cresolphthalein and then neutralize the excess alkali with tenth-normal hydrochloric acid. Each cc. of tenth-normal sodium hydroxide is equivalent to 0.014314 Gm. of trimethadione.

HYDROCHLORIDE.— $C_{16}H_{21}$ N-methyl-N'-benzyl-N'-(α -pyri-

Tripeleannamine hydrochloride occurs as a white crystalline powder possessing a bitter taste. It melts in the range 189-192.5° C. It is very soluble in water, soluble in alcohol and chloroform, and practically insoluble in benzene and ether. The pH of a 10 per cent solution is from 6.4 to 6.6.

Acidify 2 cc. of a 1 per cent solution of tripeleannamine hydrochloride with 2 drops of nitric acid. Add 5 drops of silver nitrate T.S.: a white precipitate develops, which is redissolved on the addition of a few drops of strong ammonia solution.

Add 3 drops of saturated Reinecke's salt solution to 2 cc. of a 1 per cent aqueous solution of tripeleannamine hydrochloride: a flocculent, pink precipitate develops.

Prepare the dipicrate of tripeleannamine as described in the assay for

tripelennamine the tripelennamine dipicrate melts at (constant) 185
190° C.

Calculate the tripelennamine hydrochloride content is not less than 95
per cent nor more than 102 per cent

TUAMINE (LILLY) — $C_7H_{11}N$ — M W 115.22 — d,l 2 Aminoheptane

2-Aminoheptane occurs as a colorless to pale yellow liquid which boils
within the range 139.5-142.5° C. It is sparingly soluble in water but

at 14150 to

a vapor pressure

1 per cent solution

in cyanate in 25 cc.

uric acid has been

hour, cool, filter,

10 C. the product

weighing bottle and
weigh it accurately. Evaporate the aminoheptane on a steam bath to con-
stant weight. The nonvolatile residue does not exceed 0.2 per cent.
Dissolve 1 cc. of aminoheptane in 10 cc. of liquid petrolatum U. S. P. no
turbidity is produced.

Weigh accurately about 1 gm. of aminoheptane and dissolve it in 25 cc.
of half normal sulfuric acid. Titrate the excess acid with half normal
sodium hydroxide, using methyl red T.S. as the indicator. Each cc.

packaging

TUAMINE SULFATE (LILLY) — $C_{14}H_{24}N_2H_2SO_4$ —
M W 328.51 — d,l 2-Aminoheptane sulfate

2-Aminoheptane sulfate occurs as a white crystalline powder which is
about 54

d to constant
cent

weighed the

water to which
a steam bath
ed water and

the stock solution add 1 cc. of silver nitrate T.S. a white precipitate forms, soluble in ammonia T.S.

Dry about 0.1 Gm. of d-tubocurarine chloride, accurately weighed, in a tared weighing bottle at 100° C. for four hours the loss in weight does not exceed 11.5 per cent.

Transfer 0.2 Gm. of d-tubocurarine chloride, accurately weighed, to a separatory funnel containing 200 cc. of water. Add 5 cc. of saturated sodium bicarbonate solution and extract with three 20 cc. portions of chloroform. Wash the combined chloroform extracts with 10 cc. of water, filter through a pledget of cotton into a tared beaker, evaporate and dry at 100° C. for 1 hour the weight of the residue does not exceed 3 per cent calculated on the dry basis. The residue is insoluble in water, but soluble in diluted hydrochloric acid.

Transfer about 0.15 Gm. of d-tubocurarine chloride accurately weighed, to a 100 cc. Erlenmeyer flask and add 10 cc. of water 5 cc. of diluted nitric acid and exactly 25 cc. of fiftieth normal silver nitrate. Add 5 cc. of nitrobenzene and swirl the contents of the flask to entrap the precipitate. Add 2 cc. of ferric ammonium sulfate T.S. and titrate the excess silver nitrate with fiftieth normal ammonium thiocyanate. Each cc. of fiftieth-normal silver nitrate is equivalent to 0.000709 Gm. of chlorine the

The potency of d-tubocurarine chloride is determined by observation of the "head-drop" response following intravenous injection of the drug in rabbits. (For assay methods see H. A. Holaday, U. S. Patent 2,397,417, R. F. Varney, C. R. Linegar and H. A. Holaday, *Federation Proc.*, 1, Part 1 261 (March) 1949 and G. M. Everett, *J. Pharmacol. & Exper. Therap.* 92 236 (March) 1943.)

UNDECYLENIC ACID—10-hendecenoic acid—10-undecenoic acid— $C_{11}H_{20}O_2$ —M. W. 184.27

the bromine color is discharged rapidly.

Add 1 cc. of aniline to 1 cc. of undecylenic acid and reflux for 1 hour. Cool and add 5 cc. of alcohol to the mixture and then 5 cc. of ether. Wash the ether with four 20 cc. portions of water. Evaporate the solution to dryness and recrystallize the residue from benzene. The product melts in the range 67.0°-67.5° C.

Shake 1 cc. of undecylenic acid with 20 cc. of water and then separate the solution. Add 5 drops of silver nitrate T.S. to the aqueous portion; no turbidity appears.

Shake 1 cc. of undecylenic acid with 10 cc. of water and then separate the layers. Add 1 cc. of Larium chloride T.S. to the aqueous layer; no turbidity develops.

Shake 5 cc. of undecylenic acid with 5 cc. of water and filter through a moistened paper. Add 1 drop of methyl orange T.S. to the solution and titrate with 0.1 N sodium hydroxide; no more than 0.1 cc. of 0.1 N sodium hydroxide is necessary to bring the color to that corresponding to 1 drop of methyl orange in 5 cc. of water.

Boil 1 cc. of undecylenic acid with 0.5 Gm. of sodium cathmate in 10 cc. of water; no more than a very slight opalescence appears in the hot solution.

Ash about 1 Gm. of undecylenic acid; the residue does not exceed 0.15 per cent of the weight of the original substance.

Determine the heavy metal content according to the U.S.P. XIII, p. 657; the heavy metal content does not exceed 10 ppm.

Determine the iodine value of undecylenic acid according to the U.S.P. XIII, p. 647; the iodine value is not less than 131 nor more than 138.

Weigh, accurately, about 0.5 Gm. of undecylenic acid. Titrate the acid with 0.1 N potassium hydroxide. Each cc. of 0.1 N potassium hydroxide is equivalent to 0.018427 Gm. of undecylenic acid; the undecylenic acid content is not less than 95 nor more than 108 per cent of the weighed amount.

VINBARBITAL SODIUM.— $C_{11}H_{13}N_2NaO_3$.—M. W. 246.24.—The monosodium salt of 5-ethyl-5-(1-methyl-1-butenyl) barbituric acid.

Vinbarbital sodium occurs as a white, odorless powder, possessing a bitter taste. It is soluble in alcohol and water and slightly soluble in ether and chloroform. A 1 per cent aqueous solution is alkaline to phenolphthalein and has a pH between 8.5 and 9.5.

Unbuffered aqueous solutions of vinbarbital sodium are not stable. The powder is hygroscopic and if capsules containing it are broken or exposed to high humidity the contents are affected by both moisture and carbon dioxide.

To 5 cc. of a 10 per cent solution of vinbarbital sodium slowly add 2 cc. of diluted hydrochloric acid; allow the precipitate to crystallize; filter, wash and dry at 90° C., the melting point of the vinbarbital is 161° to 163° C.

Transfer 5 cc. portions of a 10 per cent solution of vinbarbital sodium to two test tubes and to one add 1 cc. of mercuric bichloride T.S.: a white precipitate results, soluble in 10 cc. of diluted ammonia solution. To the other portion add 5 cc. of silver nitrate T.S., a white precipitate results, soluble in 5 cc. of strong ammonia solution.

Dissolve 0.1 Gm. of vinbarbital sodium in 10 cc. of distilled water, add 1 cc. of sodium hydroxide T.S. and 4 drops of potassium permanganate T.S.; a green color develops in 20 seconds, add 5 cc. of diluted hydrochloric acid the solution turns pink and a brown precipitate appears. Boil 0.5 Gm. of vinbarbital sodium with 5 cc. of 25 per cent sodium hydroxide, ammonia is evolved.

Acidify 40 cc. of a 10 per cent solution of vinbarbital sodium with diluted nitric acid and filter, separate portions of 20 cc. each of the filtrate yield no opalescence with 1 cc. of silver nitrate T.S. (chloride), no turbidity with 1 cc. of barium nitrate T.S. (sulfate); no color or precipitate on saturation with hydrogen sulfide (salts of heavy metals).

Transfer about 3 Gm. of vinbarbital sodium, accurately weighed, to a glass stoppered flask, add 50 cc. of anhydrous ether and shake for ten minutes. Decant the supernatant liquid through a filter and again extract the residue with 15 and 10 cc. portions of ether. Evaporate the combined filtered extracts to dryness in a tared beaker on the steam

... sodium, accurately weighed,
... and 10 cc. of diluted hydro-
... portions of ether, filter the
... of air
... than 89.5
... residue to
... Repeat.
... not less

than 27.5 nor more than 29.5 per cent

VITAMIN D₂.— $C_{28}H_{44}O$.—M. W. 396.63.—9,10-Ergosta-tetraene (18:10, 5:6, 7:8, 22:23)-ol-3.

Vitamin D₂ may be prepared by ultraviolet irradiation of ergosterol in a suitable solvent or by electronic bombardment of the compound: it is not identical with the vitamin D which predominates in fish liver oils and which is called vitamin D₃. A method of preparation of vitamin D₂ is given in Addendum 1936 to the British Pharmacopeia, 1932, p. 20. The crystals

have a potency of 40 units of vitamin D (U S P) per microgram. (For methods of assay see U S P)

Vitamin D₂ occurs as a colorless, odorless acicular crystalline substance. It is insoluble in water, soluble in alcohol, ether, chloroform, acetone, ethylene glycol and propylene glycol, and sparingly soluble in vegetable oils. The melting point of vitamin D₂ lies between 115° and 138° C. Solutions of vitamin D₂ possess an absorption maximum at 2,640 Å.

Dissolve about 0.5 mg. of vitamin D in 5 cc. of chloroform, add 3 drops of acetic anhydride and 3 drops of sulfuric acid and shake the mixture, a bright red color develops which rapidly changes to a color blue and finally to green.

Dissolve 30 mg. of vitamin D and 50 mg. of 3,5-dibromobenzoyl chloride in separate 1 cc. portions of anhydrous pyridine. Mix the solutions and warm the mixture on the water bath for ten minutes, add 5 cc. of water, filter and wash the precipitate repeatedly with small amounts of cold water. Recrystallize the precipitated 3,5-dibromobenzoyl derivative twice from acetone and finally dry it in a desiccator under partial vacuum. The melting point of the product is from 147° to 149° C. The specific rotation $[\alpha]_D^{25}$ of the vitamin D₂ dibromobenzoate dissolved in acetone is + 80°.

Dissolve approximately 10 mg. of vitamin D₂ in 1 cc. of alcohol and add 1 cc. of a 1 per cent solution of d-glucose in 90 per cent alcohol. Allow the mixture to stand for 12 hours. No precipitate occurs (absence of spirosterol).

Dissolve approximately 30 mg. of vitamin D accurately weighed, in 1 cc. of acetone at 25° C. Put the solution in a 0.5 decimeter tube and measure the optical rotation in a polarimeter at 25° C. using sodium light. The specific rotation lies between + 79.5 and + 81.5°. Determine the amount of carbon and hydrogen present in vitamin D₂ by burning the substance in an appropriate combustion train. The carbon content should not be less than 84.6 per cent nor more than 85.1 per cent. The hydrogen content should not be less than 10.9 per cent nor more than 11.3 per cent.

VITAMIN K₁—C₃₁H₄₆O₂—M W 450.68—2 Methyl-3-phytyl 1,4-naphthoquinone

Vitamin K₁ occurs as a yellow, very viscous, nearly odorless liquid of specific gravity about 0.967 and refractive index of 1.5250 at 25° C. It is stable in air but decomposes in sunlight. It is insoluble in water, and soluble in alcohol, benzene, chloroform, ether and vegetable oils.

Suspend one drop of vitamin K₁ in 10 cc. of methanol, add 0.3 cc. of a normal potassium hydroxide in methanol solution and shake. A deep purple color appears immediately which slowly turns to reddish blue and finally to reddish brown.

Suspend about 0.5 Gm. of vitamin K₁ in 10 cc. of methanol, add a freshly prepared solution of 0.75 Gm. sodium hydroxide (NaOH) dissolved in 2 cc. of warm water and shake vigorously for a few minutes. The oily vitamin K₁ dissolves and a reddish purple color forms which soon disappears as the mixture becomes colorless. Dilute with water, extract twice with peroxide-free ether and evaporate the ether extract under nitrogen or under vacuum. The white dihydro derivative obtained melts at 55.90° C. The dihydro derivative is readily soluble in air. Add one drop of vitamin K₁ to a mixture of 1 cc. of strong ammoniacal solution and 1 cc. of alcohol and then add one drop of ethylacetoacetate. No purple color is produced (absence of menadione). A solution of one part vitamin K₁ and 10 parts alcohol is neutral to litmus.

ZINC INSULIN CRYSTALS

—Zinc insulin crystals occur as a crystalline preparation of the active antidiabetic principle of the internal secretion of the islands of Langerhans of the pancreas. The crystals contain a small amount of zinc (not less than 0.45 per cent and not more than 0.9 per cent) which is

chemically combined with the active principle. Each milligram of the crystals is equivalent to not less than 22 units of insulin. The product is marketed in the form of crystalline zinc-insulin injection.

Zinc insulin crystals occur as small, colorless crystals which exhibit the following optical properties: uniaxial, positive; habit, flat rhombohedra, with slightly rounded edges, commonly in dual, sometimes in multiple, growths along the C axis, resembling twinning; clear and colorless; elongation of the flat rhombohedra is negative; refractive indices $n = 1.556$, $\omega = 1.545$. It is sparingly soluble in water; insoluble in alcohol, chloroform and ether; but soluble in dilute acid and dilute alkali. The isoelectric point of zinc insulin crystals is about 5.3. The crystals are stable if kept at a low temperature.

Transfer to a microscope slide approximately 0.1 mg. of zinc insulin crystals; add 0.1 cc. of distilled water; thoroughly wet the crystals by stirring with a small glass rod; the crystals do not dissolve completely but give rise to a turbid suspension; examination under the microscope shows the crystals to conform to the petrographic description of zinc insulin crystals. The crystals brown rapidly when heated above 220°C . and melt with decomposition between 230° and 240°C .

Transfer about 20 mg. of zinc insulin crystals to a platinum boat; weigh the boat and its contents within a weighing "pig"; place the boat in a vacuum desiccator over phosphorus pentoxide and dry to constant weight using the weighing "pig" to prevent the absorption of water during weighing. The loss in weight does not exceed 7.0 per cent. In the following quantitative determinations it is more convenient to weigh the zinc insulin crystals directly and to calculate the results to a dry basis rather than attempt to weigh the extremely hygroscopic dry material.

Dissolve 50 mg. of zinc insulin crystals in 5 cc. of water by the addition of sufficient tenth-normal hydrochloric acid to effect solution; transfer to a centrifuge tube and add 2 cc. of 10 per cent trichloroacetic acid with shaking, let stand ten minutes and centrifuge, decant into a 10 cc. volumetric flask, add 2 cc. of Nessler's reagent and make up to volume; allow to stand five minutes; transfer to a colorimeter and compare with a standard made up similarly and containing 0.055 mg. of ammonium sulfate; the color does not exceed that of the standard solution.

Transfer 18 mg. of zinc insulin crystals to a 100 cc. volumetric flask, add 2 cc. of tenth-normal hydrochloric acid, dilute to the mark with distilled water and shake to dissolve the crystals. Transfer 10.0 cc. of this solution to a separatory funnel, add about 20 cc. water, 10 cc. chloroform and 2 cc. dithizone reagent (prepared by dissolving 15 mg. dithizone in 100 cc. redistilled chloroform). Make the solution alkaline by the addition of ammonia water and shake until the chloroform layer is colored a clear pink. Drain the chloroform layer into a clean flask and repeatedly extract the aqueous layer with small portions of chloroform to which has been added a few drops of dithizone reagent, until the chloroform is no longer colored pink. At this point the aqueous layer may be discarded. Transfer the combined chloroform extracts to a clean separatory funnel and extract twice with 15 cc. portions of 0.02

... to remove the excess dithizone. After each extraction, add a small amount of fresh chloroform. Dry the combined chloroform extracts, reagent quality, sodium carbonate, in a 100 cc. volumetric flask, rinse the flask with chloroform and make the solution to volume with chloroform. Compare the solution in a colorimeter with a standard made as described above, using 10.0 cc. of a solution containing 0.001 mg. zinc per cubic centimeter (3.357 mg. zinc acetate $[\text{Zn}(\text{C}_2\text{H}_3\text{O}_2)_2 \cdot 2\text{H}_2\text{O}]$ per liter). The zinc content is not less than 0.45 per cent, nor more than 0.9 per cent. (An alternative method for the determination of zinc content is provided in the U. S. P. XIII, p. 727, under Zinc in Insulin Injection.)

Transfer about 10 mg. of zinc insulin crystals to a platinum dish; add two drops of concentrated sulfuric acid; ash slowly and ignite to

constant weight at 600 C. the ash is not more than 50 per cent more than the zinc sulfate calculated from the zinc content and in no case is it more than 3.30 per cent.

ZINC UNDECYLENATE.—The zinc salt of undecylenic acid.— $C_{22}H_{38}O_4Zn$.—M. W. 432.90

Zinc undecylenate occurs as a very fine white powder. It is practically insoluble in alcohol and in water.

Dissolve about 0.1 Gm of zinc undecylenate in 10 cc of water by adding 1 cc of strong ammonia solution. Add sodium sulfide T.S. a white flocculent precipitate develops.

Acidify about 0.1 Gm of zinc undecylenate with 10 cc of sulfuric acid. Extract the solution with two 25 cc portions of ether. Wash the ether solution with 3 successive 25 cc portions of water. Evaporate the ether

from 1.5 Gm of zinc undecylenate with 20 cc of water and 20 cc of hydrochloric acid. Filter the hot solution and wash the residue with about 50 cc of hot water. Make the combined filtrate and washings alkaline with ammonia T.S. and add ammonium sulfide T.S. to precipitate the zinc completely. Dilute to 200 cc, mix and filter. Add 0.5 cc of sulfuric acid to 100 cc of the clear filtrate. Evaporate to dryness and ignite to constant weight in a muffle furnace at 500° to 700° C. the weight of the residue does not exceed 7.5 mg.

Weigh, accurately about 0.25 Gm of zinc undecylenate in a tared crucible and ash the sample over a low flame to constant weight. Each 0.1 Gm of ash is equivalent to 0.531 Gm of zinc undecylenate. the zinc undecylenate content is not less than 99 nor more than 102 per cent of the dry sample.

SECTION C

Bibliographic Index to Medicinal Articles Not Included in N. N. R.

This cumulative index is intended to aid the reader in determining the status of articles which do not stand accepted by the Council and to supply him with sources of useful information on such articles. It provides a ready reference to reports of the Council on Pharmacy and Chemistry explaining the rejection of an article or the omission from New and Non-

agents not accepted for N. N. R. References to preliminary reports of the Council, which as a rule deal with new articles possessing potential acceptability for N. N. R., are not included. Information on these and on any other article or subject included in the Council's extensive files may be obtained by addressing an inquiry to the Secretary of the Council.

The references given below include: first, the date of original publication of the article in there; and, second, for the access to files of *The Journal* the article may be found the Council on Pharmacy and Chemistry, "Propaganda for Reform" and "Reports of the A. M. A. Chemical Laboratory." Council reports include reports on articles that have been considered by the Council, either at the request of the manufacturers or on the Council's own initiative. The names of the manufacturers (or their agents) follow the names of the preparations, except in those instances in which a drug is discussed in general, without reference to the product of any particular manufacturer.

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Index to Distributors

ABBOTT LABORATORIES North Chicago, Ill.—Acetarsone 186 Acriflavine,

CHLORIDE 413 VIOLETOL 304

ALLEN LABORATORIES INC Palmer Mass.—Acetarsone 186

AMEI

OSILO JU

AMES COMPANY INC Elkhart Indiana—Decholin 339 Decholin Sodium 342 Nostal 464 Pernoston 457 Pernoston Sodium 455

ARLINGTON CHEMICAL COMPANY Yonkers N. Y.—Camnoids 413 Food Epidermal and Incidental Allergens 2 Fungus Allergens 9 Pollen Allergens 11

ARMOUR LABORATORIES THE 1425 W. 42nd St. Chicago 9 Ill.—Gastric Mucin 342 Posterior Pituitary 400 Suprarenalin 235 Suprarenalin 1,000 237

ARIZOL CHEMICAL COMPANY 66 S. Franklin St. Nyack 5 N. Y.—Silver Nitrate 118

AYERST McKENNA & HARRISON LTD 22 E. 40th St. New York 16 N. Y.—Estrogenic Substances 368 Pertussis Endotoxin Vaccine with Diphtheria Toxin 307 Premarin 373

BARLOW MANN LABORATORIES INC Cedar Rapids Iowa—Aluminum Hydroxide Gel 334 Aminophylline 324

- CENTRAL PHARMACAL CO., Seymour Indiana—D g tox n 268 Sodium Ascorbate 563 Synophylate 331
- CHEMO PURO MFG CORPORATION 2632 Skillman Avenue Long Island City 1 N Y—Calcium Levulinate 421
- CIBA PHARMACEUTICAL PRODUCTS, INC Lafayette Park Summit N J—Dai 459 D g fol n 264 L po od ne, 44 L po od ne Diagnost c 399 Nupercs ne Hydrochloride 52 Pr v ne Hydrochlor de 241 Pyr benzam ne Hydrochlor de 25 Sulfanilamide 142 Sulfathiazole 147 V o form 202
- CLINADOL COMPANY INC. 572 5th Avenue New York N Y—Cod Liver Oil Concentrate 568
- COLL CHEMICAL COMPANY, 3721 27 Laclede Ave St Louis 8 Mo—Am nophyll ne 324 Ascorb c Acid 561 Chorionic Gonadotrop n 404 Diethylstilbestrol 376 Estrogen c Substances 369 Mann ol Hexan trate 275 N ac nam de 557 Sulfadiaz ne 136 Sulfathiazole 147 Thiam ne Hydrochlor de 551
- COLEMAN & BELL THE COMPANY INC Norwood Ohio—Gen an Violet 88
- COMMERCIAL SOLVENTS CORPORATION 17 E 42nd St New York N Y—Pen cillin 151 154 157 158
- CONTRA CREME AND DIAPHRAGM CO Severna Park Md—Contra Appl cator 286 Contra Creme 285
- CUTLER LABORATORIES Fourth and Parker Streets Berkeley 1 Calif—Allergen c Extracts 13 Antipertussis Serum 13
 Zn —
 Fe —
 Se —
 H —
 30 —
 To —
 48 —
- DAVIES ROSE & COMPANY LTD 22 Thayer St Boston 19 Mass—Qu n d ne Sulfate 278
- DEUTSCH SAMUEL CONVALESCENT SERUM CENTER MICHAEL REESE RESEARCH FOUND Y ON 2912 S Ellis Ave Chicago 16 Ill—Human Convalescent Measles Serum 496 Human Convalescent Scarlet Fever Serum, 496 Normal Human Plasma 475 Normal Human Serum 476
- DIARSENOL COMPANY INC 72 Kingsley St Buffalo 8 N Y—B smuth Subsalicylate, 197
- DRUG PRODUCTS CO INC THE 501 East 72nd Street New York 21 N Y—B smuth Subsalicylate 197 Diethylstilbestrol 376 Nicotinamide 557 N ketham de 231 Procaine Hydrochlor de 58 Sulfanilamide 142 Sulfathiazole 14 Thiam ne Hydrochlor de 551
- DUBIN H E LABORATORIES INC 250 E 43rd St New York 17 N Y—Am nophyll ne 324
- DUREX PRODUCTS, INC 684 Broadway New York N Y—Lact kol Creme 286 Lact kol Jelly 286 Lact kol Metric Dose Applicator 86 Lact kol Plunger Applicator 284
- DUSSEY S F & COMPANY INC 3117 21 North Third St Philadelphia 10 Pa—D g tox n 268
- DWIGHT R E AND COMPANY Plymouth Building Des Moines 9, Iowa—Ascorb c Acid 561 Menadione 571 Pen cillin 151 Thiamine Hydrochloride 551

EASTMAN KODAK COMPANY, 343 State Street, Rochester 4, N. Y.—Resorcinol Monoacetate, 124; Tetraiodophenolphthalein Sodium, 310.

EATON LABORATORIES, INC., Norwich, N. Y.—Aspogen, 337; Furacin, 91; Lorophyn Jelly, 287; Lorophyn Jelly Applicator, 287, Lorophyn Vaginal Suppositories, 290.

ENDO PRODUCTS, INC., 84-40 101st St., Richmond Hill 18, N. Y.—Allergenic Extracts, 5; Allergenic Extracts Diagnostic, 5; Aminophylline, 325; Aesculin and Ester Benzoate, 108; Chloroform, 108.

I
2
3
E
N
F
C
1
3
T

ESTRO CHEMICAL COMPANY, INC., 151 East 126th St., New York 35, N. Y.—Aminophylline, 325, Diethylstilbestrol, 376

ETHICON SUTURE LABORATORIES, Division of Johnson & Johnson, New Brunswick, New Jersey—Bio-Sorb, 439

FIRST TEXAS CHEMICAL MFG CO., Dallas, Texas—Glynazan, 332.

FLINT, EATON & COMPANY, Decatur 60, Ill.—Choline Dihydrogen Citrate, 426; Mannitol Hexanitrate, 275; Nicotinamide, 557, Nicotinic Acid, 555; Nikethamide, 281; Oleum Percomorphum, 570; Phenobarbital, 463; Sulfadiazine, 136; Sulfanilamide, 142; Sulfathiazole, 142, Thiamine Hydrochloride, 551

FORBES LABORATORIES, INC., Elgin, Illinois—Estrogenic Substances, 369.

FOUGERA, E AND CO, INC., 75 Varick St., New York, N. Y.—Lipiodol, 298, Lipiodol, 40% Iodine, 424; Lipiodol Radiologique Ascendant, 299

GALLIA LABORATORIES, INC., 254-256 West 31st St., New York 1, N. Y.—Riodine, 423

GANE AND INGRAM, INC., 43 W 16th St., New York 11, N. Y.—Aminophylline, 325, Ephedrine, 230, Ephedrine Hydrochloride, 230, Ephedrine Sulfate, 232; Mandelic Acid, 127; Phenobarbital, 463; Phenobarbital Sodium, 464, Sulfanilamide, 142.

GANE'S CHEMICAL WORKS, INC., 43 W 16th St., New York 11, N. Y.—Racephedrine, 246, Racephedrine Hydrochloride, 247; Racephedrine Sulfate, 247

GOLD LEAF PHARMACAL CO., 36 Lawton St., New Rochelle, New York—Aminophylline, 325

HAMILTON LABORATORIES, INC., THE, Asheville, North Carolina—Merphenyl Borate, 109, Merphenyl Nitrate, 110, Merphenyl Picrate, 111.

HARRIS, DR. D. L., LABORATORY, 706 Metropolitan Bldg., St. Louis 3, Mo.—Rabies Vaccine (Harris), 491

HARROWER LABORATORY, INC., THE, Glendale 5, Calif.—Aminophylline, 325, Diethylstilbestrol, 376, Nicotinamide, 557, Phenobarbital, 463, Sulfadiazine, 136, Sulfanilamide, 142, Sulfathiazole, 142, Thiamine Hydrochloride, 551

HART, E. J. & CO, LTD., 508 519 Chartres St., New Orleans 16, La.—Lac Bismo, 343.

- HARTE J F COMPANY** 1529 Broadway Detroit 26 Mich—Calcum Levulinate 421
- HEILKRAFT MEDICAL COMPANY** 331 Talbot Ave Boston Mass—Scarlet Red 80
- HEYDEN CHEMICAL CORP** 393 Seventh Ave New York 1 N Y—Penicillin 151
- HILLER LABORATORIES** 4349 N Western Ave Chicago 25 Ill—Lunosol 115
- HOFFMANN LAROCHE INC** Nutley N J—Alurate 453 Alurate Sodium 454 Dgalen, 263 Irosmgm n Bromide 255 Irosmgm n Methyl sulfate 255 Scopolamine Stable 259 Syntropan 257
- HOLLAND-RANTOS COMPANY INC** 145 Hudson St New York 13 N Y—Koromex Cream 287 Koromex Jelly 287 Koromex Vaginal Application 288
- HOLLISTER STIER LABORATORIES** 476 491 Paulsen Medical & Dental Bldg Spokane Wash—Allergenic Extracts Day ost c 6 Poison Ivy Extract 17 Poison Oak Extract 19 Tollen Extracts 13
- HORTON & CONVERSE** 621 W Pico Blvd Los Angeles 15 Calif—Sulfanilamide 143 Thiamine Hydrochloride 551
- HYLAND LABORATORIES** 4534 Sunset Blvd Los Angeles 27 Calif—Normal Human Plasma 473 Normal Human Serum 475 Peruss Immune Serum (Human) 497
- HYNSON WESTCOTT & DUNNING INC** Baltimore 1 Md—Anomony Sodium Thio glycolate 171 Anomony Thio glycollamide 170, BVL in Oil 523 Bromosulphalein Sodium 315 Glycotaurin 341 Phenol s Monothalein 311 Mercurochrome 103
- INGRAM LABORATORIES INC** 330 Front St San Francisco 11 Calif—Amnophylline 35
- INTERCHEMICAL CORPORATION BIOCHEMICAL DIVISION** 1120 Commerce Ave Union New Jersey—Eliane 414
- INTERNATIONAL VITAMIN DIVISION IVES-CAMEROY COMPANY INC** 2 E 40th St New York 16 N Y—Ascorbic Acid 561 Cod Liver Oil Concentrate Tablets 561 Halbut Liver Oil with Vitamin A 569 Nicotinic Acid 555 Nicotinic Acid Amide 557 Oenolamin A 546 Riboflavin 554 Sodium IAA 05 Thiamine Hydrochloride 551 Vitamin 564 Vitamin A and D from Cod Liver Oil 567
- JENSEN S LEBERY LABORATORIES, INC** 21st and Penn Sts Kansas City 10 Mo—Undulant Liver Vaccine 504
- JOHNSON & JOHNSON** New Brunswick New Jersey—Hemo-Pak Absorbable 437
- KINNEY AND COMPANY** Columbus Ind—Kinney's Yeast Extract 548
- KREMER URBAN COMPANY** 141 W Vine St Milwaukee 1 Wis—Amnophylline 325 Ascorbic Acid 561 Diethylstilbestrol 377 Estrone 369 Folic Acid 559 Sodium Ascorbate 563 Sodium Folate 560 Thiamine Hydrochloride 551
- LAKESIDE LABORATORIES INC** 1707 E. North Ave Milwaukee 1 Wis—Amnophylline 325 Choriongon 407 Chorionic Gonadotropin 404 Epinephrine Hydrochloride 1000 217 Epinephrine n Oil 1500 239 Estrogen Substances 370 Menadione 571 Mercubid n Sodium 317 Nicotinate 557 Nephramide 282 Penicillin 134 Pentobarbital Sodium 461, Potassium Iodide 400 Potassium Hydrochloride 60 Pyridoxine Hydrochloride 558 Sodium Morphate 219

LEDERLE LABORATORIES, DIVISION AMERICAN CYANAMID COMPANY, Pearl River, N. Y.—Aminophylline, 325; Benzestrol, 373; Diphtheria-Tetanus Toxoids, Alum Precipitated, 499; Diphtheria Toxin for Schick Test, 514; Diphtheria Toxoid, 496; Diphtheria Toxoid, Alum Precipitated, 497; Epinephrin.

Tuberculin Patch Test

LEWIS, B. L. & COMPANY, 243-250 W. Broadway, New York 13, New York—Yodoxin, 201.

LILLY, ELI & COMPANY, P.O. Box 618, Indianapolis 6, Ind.—Amytal, 452; Amytal Sodium, 453; Carbarsone, 187; Cholera Vaccine, 505; Coco-Quinine, 1; Schick Test, 514; Alum Precipitated, 498; Alum tated, 499; Ephe Estriol, 366; Est 480; Guanitol Vaccine, Types chloride, 54, Or 157, 158; Pent Propylthiouracil, 4 (Harris), 491; S Amytal, 449; Smerazine, 140, S 482; Tetanus Tox 293; Tuamine; Typhoid Vaccine, 512.

LINCOLN LABORATORIES, INC., P. O. Box 1139, Decatur, Illinois—Aminophylline, 325; Estrogenic Substances, 370; Procaine Hydrochloride, 60; Sodium Ascorbate, 563; Thiamine Hydrochloride, 551.

LIQUID CARBONIC CORPORATION, THE, MEDICAL GAS DIVISION, 3100 S Kedzie Ave., Chicago 23, Ill.—Ethylene, 39

MACALLISTER LABORATORY, 9213 Wade Park Ave., Cleveland 6, Ohio—Aluminum Hydroxide Gel, 334.

MALLINCKRODT CHEMICAL WORKS, 2nd and Mallinckrodt Sts., St. Louis 7, Mo.—Barbital, 455; Barium Sulfate, 297; Copper Citrate, 215; Hippuran, 301; Iodoikon, 310; Iso-Iodoikon, 314; Mandelic Acid, 127; Mercuric Cyanide, 100; Phenobarbital Sodium, 464; Quinidine, 276; Quinidine Sulfate, 277; Quinine Ethyl Carbonate, 169; Urea, 321; Zinc Peroxide, 122

MALTRIE CHEMICAL CO., THE, 246-250 High St., Newark 2, N. J.—Ephedrine Sulfate, 232; Sulfanilamide, 143; Sulfathiazole, 142.

MANHATTAN EYE SALVE CO., INC., Louisville, Ky.—Butyn Sulfate, 51; Copper Citrate, 215; Holocaine, 57; Yellow Oxide of Mercury, 102.

MASSENGILL, S. E., COMPANY, Bristol, Tennessee—Aminophylline, 325; Ephedrine Sulfate, 232; Hexestrol, 381; Methadone Hydrochloride, 31; Sulfamerazine, 140.

McKESSON & ROBBINS, INC., Bridgeport 9, Conn.—Ascorbic Acid, 561; Halibut Liver Oil with Viosterol in Oil, 569; Oleo Vitamins A and D, 566; Thiamine Hydrochloride, 551; Viosterol, 565.

NATIONAL ANILINE DIVISION, ALLIED CHEMICAL AND DYE CORPORATION,
40 Rector St., New York 6, N. Y.—Acridavine, 83; Acridavine
Hydrochloride, 84; Gentian Violet, 88; Phenolsulfonphthalein, 312;
Proflavine, 85; Scarlet Red, 80; Scarlet Red Sulfonate, 81; Succin-
chlorimide, 96.

NATIONAL DRUG CO., THE, 4664-85 Stenton Ave., Philadelphia 44, Pa.—
Allergenic Extracts, 14; Ascorbic Acid, 561; Diphtheria and Tetanus
Toxoids, Alum Precipitated, 499; Diphtheria-Tetanus-Pertussis Com-
bined Vaccine, 509; Diphtheria Toxin for Schick Test, 514; Diph-
theria Toxoid, 496; Diphtheria Toxoid, Alum Precipitated, 498;
Diphtheria Toxoid, Alum Precipitated and Pertussis Vaccine Com-
bined, 507; Ephedrine Sulfate, 232; Estronol, 370; Gas Gangrene
Antitoxin, 481; Influenza Virus Vaccine, Types A and B, 490;
Mannitol Hexanitrate, 275; Nicotinic Acid, 556; Nikethamide, 291;
Pertussis Vaccine, 506; Pertussis Vaccine, Alum Precipitated, 506;
Rabies Vaccine, 492; Scarlet Fever Streptococcus Toxin, 493;
Scarlet Fever Streptococcus Toxin for the Dick Test, 493; Sodium
Morrhuate, xoid-
Vaccine, 51 oxin,
482; Tetanus ide,
552; Typhoid

NOVOCOL CHEMICAL MFG. CO. INC., 2911-23 Atlantic Ave., Brooklyn 7,
N. Y.—Amylsine Hydrochloride, 49; Monocaine Formate, 55; Mono-
caine Hydrochloride, 56

OHIO CHEMICAL & MFG CO., THE, 1400 E. Washington Ave., Madison
10, Minn.—Cyclopropane, 38; Ethylene Gas, 39.

ORTHO PHARMACEUTICAL CORPORATION, Raritan, N. J.—Hexestrol, 385;
Ortho-Creme, 288; Ortho-Gynol Vaginal Jelly, 289; Ortho Vaginal
Applicator, 289.

PARKE, DAVIS & COMPANY, Detroit 23, Mich.—Adrenalin, 235; Adrenalin
Chloride 1:100, 241; Adrenalin Chloride 1:1,000, 237; Adrenalin in
Oil 1:500, 239; Allergenic Extracts, Diagnostic, 7; Ascorbic Acid,
Oil 1:500, 239; Bismuth Viosterol, 99; Bis-

.
th Viosterol,
499; Diph-
theria
ssis Vaccine,
233; Ergot
e Antitoxin,
r Oil with
e Acid, 556;
ssis Vaccine,
ol Chloride,
3; Pituitrin,
101; Sal-
treptococcus
94; Scarlet
et Red, 81;
501; Sulfal-
ulfathiazole,
xoid, Alum
ismol, 195,
Test, 520;
Test, 520;
accine, 512.

Tuberculin, Purified Protein Extract, 565;
Tyrothricin, 72; Ventriculin, 357; Viosterol, 565.

PATCH, E. L., THE, Stoneham Post Office, Boston, Mass.—Alinox, 337;
Glythconate, 332; Kondremul, 344.

PAUL-LEWIS LABORATORIES, INC., 4253 N. Port Washington Road, Mil-
waukee 12, Wis.—Calcium Levulinate, 421.

SCHENLEY LABORATORIES, INC., 350 Fifth Ave., New York 1, N. Y.—Penicillin, 152, 157, 158

SCHERING CORPORATION, 2 Broad St., Bloomfield, N. J.—Estinyl, 380; Neo-Iopax, 308; Priodax, 302.

SCHERING & GATZ, INC., 113 W. 18th St., New York, N. Y.—Euphthalmine Hydrochloride, 257; Iocamsen, 96; Medinal, 455; Urotropin, 129; Xeroform, 100

SCHIEFFELIN & Co., 16-30 Cooper Square, New York 3, N. Y.—Aluminum Hydroxide Gel, 335; Ascorbic Acid, 562; Benzeestrol, 373; Dicumtarol, 348; Sulfanilamide, 143; Sulfathiazole, 143; Thiamine Hydrochloride, 552.

SCHMID, JULIUS, INC., 423 W 55th St., New York 19, N. Y.—Ramses Vaginal Applicator, 290; Ramses Vaginal Jelly, 289

SEARLE, G. D. & Co., Post Office Box 5110, Chicago 80, Ill.—Aminophyllin, 327; Bismuth Sodium Tartrate, 194; Diodoquin, 201; Gold Sodium Thiosulfate, 526, Metamucil, 346, Sodium Morrhuate, 219

SEYDEL CHEMICAL COMPANY, 225 Mercer St., Jersey City 2, N. J.—Benzyl Alcohol, 49.

SHARP & DOHME, INC., Glenolden, Pa.—Antivenin (*Latrodectus mactans*), 478; Bl...
Gonadotropin, (Sulzberger),
Pertussis Antitoxin, 503.
Diphtheria Toxin, 494; Searle
515; Silver Nitrate
Sulfadiazine, 146,
merazine, 146, Star
merazine, 140; Sulf
143; Sulfathalidine,
Tyrothricin, 72.

SMITH, CARROLL DUNHAM, PHARMACAL CO, New Brunswick, N. J.—
Ascorbic Acid, 562; Bistrimate, 196; Calcium
strol, 377; Digoxin,
271; Penicillin, 157;
; Sulfanilamide, 143;

SMITH-DORSEY COMPANY, Lincoln, Nebr.—Aminophylline, 327; Ascorbic Acid, 562, Bismuth Subsalicylate, 197; Diethylstilbestrol, 377; Ephedrine Sulfate, 233; Epinephrine in Oil, 1 500, 239, Estrogenic Substances, 371, Liquid Petrolatum, 344, Mannitol Hexantrate, 275; Menadione, 571; Nicotinic Acid, 556; Nikethamide, 281; Penicillin, 157, Phenobarbital, 463, Pyridoxine Hydrochloride, 558; Sulfadiazine, 137; Sulfanilamide, 139, Sulfathiazole, 143; Thiamine Hydrochloride, 552

SMITH, KLINE & FRENCH, Laboratories, 5th and Arch Sts., Philadelphia 5, Pa.—Benzedrine, 225; Benzedrine Sulfate, 227.

SMITH OIL & REFINING CO, Rockford, Ill.—Mineral Oil, 345.

SMITH, UPSHER, Co., 529 So Seventh St., Minneapolis, Minn.—Pyrethrum, 123.

SPECIAL FORMULA CORPORATION 445 Park Ave. New York 22, N. Y.—
Lygel Vaginal Applicator 298 Lygel Vaginal Cream 238 Lygel
Vaginal Jelly 288 Lygones Vaginal Suppositories 291

SQUIBB E. R. & SONS, 745 Fifth Ave. New York 22, N. Y.—Amphotericin
373 Ascorbic Acid 567 Brewer's Yeast 549 Chlorarsen 180 Cod
Liver Oil with Viosterol 367 Cyclopropane 38 Diethylstilbestrol
378 Diphtheria and Tetanus Toxoid Alum Precipitated and Pertussis
Vaccine Combined, 508 Diphtheria Toxin for the Schick Test 514
Diphtheria Toxoid, 497 Diphtheria Toxin Alum Precipitated 498
Diphtheria Toxoid Tetanus Toxoid Alum Precipitated 500 Folliculin
405 Gas Gangrene Antitoxin 481 Globulin Insulin with Zinc 337
Influenza Virus Vaccine Types A and B 490 Insulin 390 Intocoxin
211 Iodobismutol 199 Iprat Calcium 466 Iprat Sodium
466 Mannitol Hexantrate 335 Penicillin 152 155
Pituitary 401, Procaine 1
392 Rabies Vaccine (Semple)
Vaccine 511 Scarlet Fever
Streptococcus Toxin for the Dick Test 515 Sodium Sulfadiazine
Sterile, 146 Streptomycin 163 Sulfadiazine 137 Sulfaguanidine
138 Sulfamerazine 140 Sulfathiazole 143 Tetanus Gas Gangrene
Antitoxin 482 Tetanus Toxoid, Alum Precipitated 503 Thiamine
Hydrochloride 552 Thyloquinone 372 d-Tubocurarine Chloride
213 Viosterol 365

STERONE CHEMICAL CO. INC. 8471 Parsons Blvd. Jamaica 2, New
York—Penicillin, 156

STRASSENBURGH R. J., COMPANY Rochester New York—Digitoxin 268
Folic Acid 559

SYNTAM LABORATORIES, 4630 27th St., Long Island City 1, N. Y.—
Chlorguanide Hydrochloride 164

THOMSON MARVIN R. INC., 67 Greenwich Ave. Stamford, Conn.—
Vitamin B complex 549

ULMER PHARMACEUTICAL COMPANY 412 So. 6th St., Minneapolis Minn.—
Sodium Morrhuate 219

U. S. STANDARD PRODUCTS CO. Woodworth Wis.—Allergenic Extracts
15 Diphtheria Toxoid, 497 Diphtheria Toxoid Alum Precipitated,
498 Typhoid Hydrochloride 11000 238 Posterior Pituitary
401 Procaine Hydrochloride 62 Rabies Vaccine (Semple) 492
Scarlet Fever Streptococcus Toxin 494 Scarlet Fever Streptococcus
Toxin for the Dick Test 516 Tetanus-Gas Gangrene Antitoxin 482
Typhoid Vaccine 512

U. S. VITAMIN CORPORATION, 250 East 43rd St. New York 17, New
York—Ascorbic Acid 562, Menadione 572 Nicotinamide 556 Nicotinic
Acid 557 Pyridoxine Hydrochloride 558 Riboflavin 554 Thiamine
Hydrochloride 552

UTJOHN COMPANY THE Kalamazoo 99 Mich.—Adrenal Cortex 361
Aluminum Hydroxide Gel 333 Ascorbic Acid 562

143 Sulfathiazole 143 Thiamine Hydrochloride 553

VALE CHEMICAL CO., INC., THE, 814-816 Gordon St., Allentown, Pa.—Aminophylline, 327; Diethylstilbestrol, 378; Menadione, 572; Nicotinamide, 558; Phenobarbital, 463; Sulfadiazine, 137; Sulfathiazole, 143; Thiamine Hydrochloride, 553.

VARICK PHARMACAL CO., INC., 75 Varick St., New York 13, N. Y.—Digitaline Nativefle, 268.

VI-CO PRODUCTS COMPANY, 415 W. Scott, Chicago 10, Ill.—Vitamin B Complex, 549.

WALKER VITAMIN PRODUCTS, INC., Mount Vernon, N. Y.—Ascorbic Acid, 562, Folic Acid, 559, Hexavitamin, 574; Niacinamide, 558; Nicotinic Acid, 556, Oleo Vitamin A, 546; Oleo Vitamin A-D, 566; Riboflavin, 555, Thiamine Hydrochloride, 553; Vitamin C Drops, 561.

WALLACE & TIERNAN PRODUCTS, INC., Belleville 9, N. J.—Azochloramide, 93, Desenex, 119; Monomestrol, 382, Sodium Sotradecol, 221

WARNER, WILLIAM R. & CO., INC., 113 W. 18th St., New York 11, N. Y.—Nikethamide, 281, Penicillin, 153.

WATSON-TOWN DRUGS COMPANY, 592 W. Goodale St., Columbus 8, Ohio—Ascorbic Acid, 562, Diethylstilbestrol, 378; Epinephrine Hydrochloride, 230; Nicotinamide, 558; Sodium, 465; Posterior Pituitary, 401; Sulfathiazole, 143; Thia-

WERNER DRUG & CHEMICAL CO., 759 Beechwood Ave., Cincinnati 32, Ohio—Eucastropine Hydrochloride, 258; Phenacaine Hydrochloride, 57.

WHITE LABORATORIES, INC., 113 N. 13th St., Newark, N. J.—Cod Liver Oil Concentrate, 568; Cod Liver Oil Concentrate Tablets, 568, Dienestrol, 374, Oleo-Blend Vitamin A, 546; Thiamine Hydrochloride, 553.

WHITTAKER LABORATORIES, INC., 898 Washington St., Peekskill, N. Y.—Cooper Creme, 290; Cooper Creme Dosimeter, 290.

WILSON LABORATORIES, DIVISION OF WILSON & CO., INC., 4221 S. Western Ave., Chicago 9, Ill.—Epinephrine, 230; Epinephrine Hydrochloride 1 1,000, 238, Gastric Mucin, 343; Posterior Pituitary, 401.

WINTHROP-STEARNS, INC., 170 Varick St., New York 13, N. Y.—Adanon Hydrochloride, 31; Anaesthesia, 48; Aralen Diphosphate, 165; Aristof, 92, Ascorbic Acid, 562; Avertin, 167; Creamals Hydrochloride, 167; Concentrated Gastric Luminol, Neosalva 243; Nov 159, Phosphamide 320, Ski Sulfathiazole, 143; Thiamine Hydrochloride, 553.

WYETH, INCORPORATED, 1600 Arch St., Philadelphia 3, Pa.—Allergenic Extract, 16, Aminophylline, 328; Ascorbic Acid, 562; Bornate, 120; Carbomol, 437, Carotene, 545, Conestron, 373; Diphtheria-Tetanus Toxoid, Alum Precipitated, 500; Diphtheria Toxin for the Schick Test, 514, Diphtheria Toxoid, 497; Diphtheria Toxoid, Alum Pre-

WYETH INCORPORATED—(Continued)

c p tated, 498 Gas Gangrene Ant iox n 481 Immune Serum Globul n
 (Human) 474 Lactam n 415 Meon ne 416 Neohetramine Hydro-
 chlor de 24 Pen c il n 153 Ictrogalar 345 Phosphaljel 335
 Picragol 119 Prote n Extracts Diagnost c ? Rab es Vaccine (Chlo-
 roform K Red) 49 Rab es Vaccine (Simple) 492 Pertuss s
 Vaccine 506, Purod g n 268 Pyr dox ne Hydrochloride 518
 Sod um PABA 205 Scarlet Fever Streptococcus Tox n for the Dick
 Test 516 Scarlet Fever Streptococcus Tox n Tannic Acid Pre-
 c p tated 495 Tetanus Gas Gangrene Ant iox n 433 Tetanus
 Toxo d Alum Precipitated 503 Thiam ne Hydrochlor de 553

ZEMMER COMPANY INC THE 3943 57 Sennott St Oakland Station
 Pittsburgh 13 Pa —Am nophyll ne 328

Allergenic Extract—(Continued)

	PAGE
Extracts (Endo)	5
Extracts (National Drug)	14
Extracts (Pitman Moore)	14
Extracts (U. S. Standard Prod.)	15
"	5
"	6
"	7
"	7
"	1
"	1
"	33
"	415
"	410
"	415
"	413
"	337
"	413
"	322
"	324
(Barlow-Money)	324
(Barry)	324
(Bischoff)	324
(Breon)	324
(Brewer)	324
(Bristol)	324
(Cole)	324
(Dubin)	324
(Endo)	325
(Estro)	325
(Gane & Ingram)	325
(Gold Leaf Pharmacal)	325
(Harrower)	325
(Ingram)	325
(Kremers-Urban)	325
(Lakeside)	325
(Lederle)	325
(Lincoln)	325
(Massengill)	325
(Merck)	326
(Merrell)	326
(Miller)	326
(Pharmedic)	326
(Premo)	326
(Raymer)	326
(Rorer)	327
(Searle)	327
(Carroll) Dunham Smith)	327
(Smith-Dorsey)	327
(Vale)	327
(Warren-Teed)	328
(Wyeth)	328
(Zemmer)	328
Aminopyrine	33
(Abbott)	34
(Merck)	34
(Merrell)	34
Amniotin (Squibb)	371
Amobarbital	451, 577
Sodium	452, 578
Amphetamine	224, 579
Racemic	224
Sulfate	225, 579
Sulfate, Racemic	225
Amprotopine Phosphate	256, 580
Amylsine Hydrochloride	48, 580
(Novocol)	49
Amytal (Lilly)	452
Sodium (Lilly)	453

GENERAL INDEX

- Anaesthesia (Winthrop-Stearns)
- Analgesics
 - Nonopiate Addicting
- Anayodin (Dischoff)
- Anesthetics
 - General
 - Local
 - Local Slightly Soluble
 - Local, Soluble
- Anesthin (Abbott)
- Anionic, Surface Active Anti Infectives
- Antacids
- Anthelmintic Agent
- Anthracene Derivatives
- Anthralin
 - (Abbott)
- Antibacterial Agents
 - Serums
- Antibiotics
- Antibodies Naturally Produced
- Anticoagulants
- Anti Erysipeloid Serum
 - Serum (Pitman Moore)
- Anti Infectives Cationic Surface Active
 - Local
 - Surface Active
 - Systemic
- Antimalarial Agents
 - Agents, Naturally Occurring Compounds
 - Agents Synthetic Compounds
- Antimony Compounds
 - Sodium Thioglycollate
 - Sodium Thioglycollate (H W & D)
 - Thioglycollamide
 - Thioglycollamide (H W & D)
- Antiparasympathomimetic Agents
- Antipertussis Serum (Human) (Cutter)
- Antiprotozoan Agents
- Antirickettsial Agent
- Antismallpox Vaccine
- Antispasmodic Preparations
- Antitetanic Globulins
 - Serum Purified
- Antithyroid Drugs
- Antitoxic Serums
- Antitoxins
- Antivenin (Crotalus)
 - (Lactrodectus mactans)
 - (Lactrodectus mactans) (S & D)
- Aprobarital
 - Sodium
- Aralen Diphosphate (Winthrop Stearns)
- Argyn (Abbott)
- Aristol (Winthrop-Stearns)
- Arsenic Compounds
 - Pentavalent Compounds Containing
 - Trivalent Compounds Containing
- Arsphenamine
 - (Merck)
- Ascorbic Acid
 - Acid
 - Acid (Abbott)
 - Acid (American Pharm)
 - Acid (Breon)
 - Acid (Burlington's)
 - Acid (Burroughs Wellcome)
 - Acid (Cole)

2

170

453

453

GENERAL INDEX

Ascorbic Acid—(Continued)		PAGE
Acid (Endo)	561	561
Acid (Harrower)	561	561
Acid (International Vitamin)	561	561
Acid (Kremers-Urban)	561	561
Acid (McKesson & Robbins)	561	561
Acid (Mead Johnson)	561	561
Acid (Merrell)	561	561
Acid (Muller)	561	561
Acid (National Drug)	561	561
Acid (P. D. & Co.)	561	561
Acid (Pitman-Moore)	561	561
Acid (Premo)	562	562
Acid (Schieffelin)	562	562
Acid (Carroll Dunham Smith)	562	562
Acid (Smith-Dorsey)	562	562
Acid (Squibb)	562	562
Acid (U. S. Vitamin Corp.)	562	562
Acid (Upjohn)	562	562
Acid (Walker)	562	562
Acid (Warren-Teed)	562	562
Acid (Winthrop Stearns)	562	562
Acid (Wyeth)	562	562
Acid Preparations	560	560
Aspogen (Eaton)	337	337
Astringents, Caustics and Sclerosing Agents	214	214
Atabrine di-Hydrochloride (Winthrop Stearns)	167	167
Atropine Derivatives and Analogues	256	256
Attenuated Living Viruses or Killed Viruses	489	489
Autonomic Drugs	222	222
Avertin with Amylene Hydrate (Winthrop-Stearns)	41	41
Azo Compounds	79	79
Azochloramid (Wallace & Tiernan)	93	93
Bacilli Emulsion	520	520
Bacterial Toxins	493	493
Toxins, Modified	495	495
Vaccines	503	503
Bal in Oil (H. W. & D.)	523	523
Barbital	454	454
(Abbott)	455	455
(Mallinckrodt)	455	455
(Merck)	455	455
Sodium	455	455
Sodium (Merck)	455	455
Soluble	455	455
Barbitone	454	454
Soluble	455	455
Barbituric Acid Derivatives	447	447
Barium Sulfate	296	296
Sulfate (Mallinckrodt)	297	297
Sulfate (Merck)	297	297
Bazillanemulsion, Koch	520	520
Benadryl Hydrochloride (P. D. & Co.)	24	24
Benylate (Breon)	123	123
Benzalkonium Chloride	75	75
Benzadrine (S. K. & F.)	225	225
Sulfate (S. K. & F.)	227	227
Benzestrol	373, 584	373, 584
(Lederle)	373	373
(Schieffelin)	77, 584	77, 584
Benzethonium Chloride	48	48
Benzocaine (Merck)	295	295
	49	49
	49	49
	122	122
	552	552
Betabon (Mallinckrodt)	399	399
Beta-Hypophamine	399	399
Tannate		

GENERAL INDEX

Bile Salts (Winthrop-Stearns)	
Bilein (Abbott)	
Bio Sorb (Ethicon Suture)	
Bismarsen (Abbott)	
Bismo Cymol (Abbott)	
Bismuth Metal Compounds	179
Arsphenamine Sulfonate	192
Camphocarboxylate	
Compounds	193
Ethylcamphorate	
Ethylcamphorate (Upjohn)	
Magma	
Nitrate, Basic	
Paste, Surgical (P D & Co)	
Potassium Tartrate	
Potassium Tartrate (Abbott)	
Potassium Tartrate (Brewer)	
Sodium Iodide	194
Sodium Tartrate	
Sodium Tartrate (Searle)	195
Sodium Thio glycollate	193
Sodium Trisglycollamate	
Subnitrate	
Subsalicylate	
Subsalicylate (Abbott)	
Subsalicylate (Diarsenol)	
Subsalicylate (Endo)	
Subsalicylate (Merck)	
Subsalicylate (P D & Co)	
Subsalicylate (Smith Dorsey)	
Subsalicylate (Upjohn)	99
Tribromophenate	
Trisinate (Carroll Dunham Smith)	
Bivalent Gas Gangrene Antitoxin	
Blood Derivatives, Normal or Normal Serums	
Group Specific Substances A and B	
Group Specific Substances A and B (S & D)	
Bornate (Wyeth)	
Boro Chlorotone (P D & Co)	
Botulism Antitoxin	
Brain Extract Solution	
Lipoid	
Brewer's Yeast (Abbott)	
Yeast (McNeil)	
Yeast (Mead Johnson)	
Yeast (Squibb)	
Brilliant Green	
Bromine Compounds Containing	440
Bromisovalum	
Bromsulphatein Sodium (H W & D)	
Bromural (Bilhuber Knoll)	566
Brucella Vaccine	
Burbot Liver Oil	
Liver Oil (Burbot Liver Prod)	456
Butabarbital Sodium	
Butacaine Sulfate	43
Butallylonal	44
Butamben Picrate	
Butesin (Abbott)	
Picrate (Abbott)	45
Butethal	5
Butethamine Formate	
Hydrochloride	
Butisol Sodium (McNeil)	
Butyl Aminobenzoate	44
Butylchloral Hydrate	
Butyn Sulfate (Abbott)	
Sulfate (Manhattan Eye)	

	PAGE
Calcium Compounds	418
Iodobehenate	423
Levulinate	420
Levulinate (Chemo Puro)	421
Levulinate (Hartz)	421
Levulinate (Paul Lewis)	421
Levulinate (Carroll Dunham Smith)	421
Monoiodobehenate	423
Probarbital	465
Caminoids (Arlington)	413
Carbarsone	186
(Lilly)	187
Carbol-fuchsin Paste	97
Carbon Tetrachloride	206
(Merck)	206
Carbowax 1500 (Carbide & Carbon)	434
1540 (Carbide & Carbon)	435
4000 (Carbide & Carbon)	435
Carbromal	441
(Merck)	441
(Upjohn)	441
Cardiovascular Agents	260
Carfusin (Rorer)	87
Carotene	544
(Wyeth)	545
Castor Oil, Iodinated	423
Caustics, Astringents and Sclerosing Agents	214
Cebione (Merck)	561
Ceepryn Chloride (Merrell)	78
Cellulosic Acid	436, 645
Central Nervous System Stimulants	278
Cephalin, Impure	352
Cetyl Pyridinium Chloride	78, 597
Cevitaminic Acid	537
Chaulmoogra Derivatives	126
Chinioson	200
(Abbott)	200
(Endo)	201
(Winthrop-Stearns)	201
Chloral Derivatives	441
Chloramine	91
-T	91
Chlorazene (Abbott)	92
Chloretone (P. D. & Co.)	443
Chlorguanide Hydrochloride	163, 597
(Abbott)	164
(Syntam)	164
Chlorine Derivatives	91
Chloroazodin	92
Chlorobutanol	442
(Merck)	443
Chloroquine Diphosphate	164, 598
n-Chlorosuccinimide	95
Cholera Vaccine	504
Vaccine (Lilly)	505
Choleretics	338
Choline Dihydrogen Citrate	425, 599
Dihydrogen Citrate (Flint, Eaton)	426
Chondodendron Tomentosum Extract, Purified	209, 600
Choriogonin (Lakeside)	404
Choriomic Gonadotropin	403
Gonadotropin (Breon)	404
Gonadotropin (Cole)	404
Gonadotropin (Lakeside)	404
Gonadotropin (S. & D.)	404
Citrated Normal Human Plasma	474
Clorarsen (Squibb)	180
Coco-Quinine (Lilly)	170

GENERAL INDEX

781

	PAGE
Cod Liver Oil	566
Liver Oil Concentrate (Chinadol)	568
Liver Oil Concentrate (Liduol)	567
"	568
"	568
"	568
"	567
"	567
"	567
"	567
"	570
"	440
Contra (Wyeth)	566
Contra Applicator (Contra Creme & Diaphragm)	566
Creme (Contra Creme & Diaphragm)	484
Contraceptives	373
• Capsules and Suppositories	286
Criteria for Acceptability	285
Criteria for Acceptability	283
• Agents and Syringe Applicators and Nozzles	290
• Criteria for Acceptability, Diaphragm or Cap	283
Jellies and Creams	283
Preparations	283
Cooper Creme (Whittaker)	285
Creme Dosimeter (Whittaker)	285
Citrate (Manhattan Eye)	285
Salts	290
Comparadinate	290
Copper Citrate (Mallinckrodt)	215
Creamalin (Winthrop-Stearns)	215
Cremo-Bismuth (S & D)	600
Cresal n Metacresylacetate Sulzberger (S & D)	215
Cresol and Derivatives	335
meta Cresylacetate	343
Crotalus Antitoxin	73
Croton Chloral Hydrate	73
Crystal Violet	600
Cupric Citrate	477
Curare	598
Cyclobarbitol	87
Cyclohexenylethyl Barbituric Acid	215
Cyclopropane	208
(Ohio Chemical)	601
(Squibb)	458
Decholin (Ames)	458
Sodium (Ames)	36
Dehydrochloric Acid	38
(Breon)	38
(Harrower)	339
(Miller)	342
Demerol Hydrochloride (Winthrop-Stearns)	338, 601
Desenex (Wallace & Tiernan)	340
Desoxyn Hydrochloride (Abbott)	340
Dextrose	340
Solution 50%	31
Diagnostic Agents	119
Aids	28
Aids External	424
Aids Internal	217
Dial (Ciba)	513
Diallylbarbituric Acid	292
Diallylmalonylurea	292
Dibucaine Hydrochloride	293
	439
	458
	602
	458
	514
	602

	PAGE
Dichloramine	93
-T	93
-T (Abbott)	94
"	180
"	180
"	181
"	493
Dicumarol	
(Abbott)	347, 603
(Merrell)	348
(Scheffelin)	348
Dienestrol	349
(Rare Chemicals)	
(Carroll Dunham Smith)	
(White)	
Diethylbarbiturate Sodium	455
Diethylbarbituric Acid	454
Diethylmalonylurea	454
Sodium	455
Diethylstilbestrol	374
(Abbott)	376
(American Pharm)	376
(Bio-Intrasol)	376
(Cole)	376
(Drug Products)	376
(Endo)	376
(Estro)	376
(Harrower)	377
(Kremers-Urban)	377
(Lilly)	377
(Merrell)	377
(Miller)	377
(Premo)	377
(Rorer)	377
(Carroll Dunham Smith)	377
(Smith-Dorsey)	377
(Squibb)	378
(Upjohn)	378
(Vale)	378
(Warren Teed)	378
(Winthrop-Stearns)	378
Dipalmitate	678
Dipropionate	378, 604
Dipropionate (Blue Line)	379
Dipropionate (Breon)	379
Dipropionate (Winthrop-Stearns)	379
Monomethyl Ether	381
Diethylsulfonmethylethylmethane	446
Digalen	263, 605
(Hoffmann-LaRoche)	263
Digifolin	263, 605
(Ciba)	264
Digilanid	264, 605
(Sandoz)	265
Digitaline Native (Varick Pharmacal)	268
Digitalis and Digitalis-like Principles and Preparations	260
Digitalis Principles, Related	266, 606
Digitalan	266
(Merck)	266
Digitol	266
(S & D)	267
Digitoxin	268
(Abbott)	268
(Central Pharmacal)	268
(Durst)	268
(McNeil)	268
(Premo)	268

Digitoxin—(Continued)	PAGE
(Carroll Dunham Smith)	268
(Strassenburgh)	268
Digoxin	268
(Burroughs Wellcome)	269
Dihydrocodeinone Bitartrate	28, 606
Dihydromorphinone Hydrochloride	29
Dihydroxy Aluminum Ammonioacetate	336, 607
Duodo-Hydroxyquinoline	201, 608
Dilantin Sodium (P D & Co.)	444
Dilaudid Hydrochloride (Bilhuber Knoll)	29
2,3-Dimercaptopropanol in Oil	522 609
Diodoquin (Searle)	201
Diodrast (Winthrop Stearns)	306
Compound Solution (Winthrop-Stearns)	307
Concentrated Solution (Winthrop-Stearns)	304
Diothane (Merrill)	52
Hydrochloride (Merrill)	53
Diperodon	52, 609
Diperodon Hydrochloride	53, 610
Diphenhydramine Hydrochloride	21, 611
Diphenylhydantoin Sodium	443
Sodium (American Pharm)	444
Sodium (Prenco)	444
Diphtheria Antitoxin	479
Pertussis Antigen Combined Alum Precipitated (S & D)	508
Tetanus Pertussis Antigen Combined Alum Precipitated (S & D)	508
Tetanus Pertussis Combined Vaccine Alum Precipitated (National Drug)	508
and Tetanus Toxoids Alum Precipitated	499
Tetanus Toxoids Alum Precipitated (Lederle)	499
Tetanus Toxoids Alum Precipitated (Lilly)	499
and Tetanus Toxoids Alum Precipitated (National Drug)	499
Tetanus Toxoids Alum Precipitated (P D & Co.)	499
and Tetanus Toxoids Alum Precipitated (Pitman-Moore)	500
Tetanus Toxoids Alum Precipitated (S & D)	500
Tetanus Toxoids Alum Precipitated (Squibb)	500
Tetanus Toxoids Alum Precipitated (Wyeth)	500
and Tetanus Toxoids Alum Precipitated and Pertussis Vaccine Combined (Squibb)	508
Toxin Antitoxin Mixture	495
Toxin Diagnostic	513
Toxin for the Schick Test	513
Toxin for the Schick Test (Cutter)	513
Toxin for Schick Test (Lederle)	514
Toxin for Schick Test (Lilly)	514
Toxin for Schick Test (National Drug)	514
Toxin for Schick Test (P D & Co.)	514
Toxin for the Schick Test (Pitman Moore)	514
Toxin for the Schick Test (S & D)	514
Toxin for the Schick Test (Squibb)	514
Toxin for the Schick Test (Wyeth)	514
Toxoid	496
Toxoid (Cutter)	496
Toxoid (Lederle)	496
Toxoid (Lilly)	496
Toxoid (National Drug)	496
Toxoid (P D & Co.)	497
Toxoid (S & D)	497
Toxoid (Squibb)	497
Toxoid (U S Standard Prod.)	497
Toxoid (Wyeth)	497
Toxoid Alum Precipitated	497
Toxoid Alum Precipitated (Lederle)	497
Toxoid Alum Precipitated (Lilly)	498
Toxoid Alum Precipitated (National Drug)	498
Toxoid Alum Precipitated (P D & Co.)	498
Toxoid Alum Precipitated (Pitman Moore)	498

Diphtheria Antitoxin—(Continued)		PAGE
Toxoid, Alum Precipitated (S. & D.)	498	498
Toxoid, Alum Precipitated (Squibb)	498	498
Toxoid, Alum Precipitated (Squibb)	498	498
		507
		508
		619
		316
Dried Yeast	547	547
Drisdol (Winthrop-Stearns)	565	565
Drugs, Gastro-intestinal	333	333
Dry Yeast	547	547
Dyes	79	79
Phenolphthalein	308	308
Dymixal	84, 612	84, 612
(McNeil)	85	85
Elamine Lyophilized (Interchemical)	414	414
Emollients	442	442
Entromone (Endo)	404	404
Ephedrine	228	228
(Abbott)	230	230
(Gane & Ingram)	230	230
(Merck)	230	230
Hydrochloride	230	230
Hydrochloride (Abbott)	230	230
Hydrochloride (American Pharm.)	230	230
Hydrochloride (Gane & Ingram)	230	230
Hydrochloride (Lilly)	231	231
Hydrochloride (Merck)	231	231
Hydrochloride (P. D. & Co.)	231	231
Hydrochloride (Pitman-Moore)	231	231
Hydrochloride (Warren-Teed)	246	246
Hydrochloride, Racemic	246	246
Racemic	231	231
Sulfate	231	231
Sulfate (Abbott)	231	231
Sulfate (American Pharm.)	231	231
Sulfate (Burroughs Wellcome)	232	232
Sulfate (Endo)	232	232
Sulfate (Gane & Ingram)	232	232
Sulfate (Harrower)	232	232
Sulfate (Lilly)	232	232
Sulfate (Maltbie)	232	232
Sulfate (Massengill)	232	232
Sulfate (Merck)	232	232
Sulfate (Merrell)	232	232
Sulfate (Miller)	233	233
Sulfate (National Drug)	233	233
Sulfate (P. D. & Co.)	233	233
Sulfate (Premo)	233	233
Sulfate (Rorer)	233	233
Sulfate (S. & D.)	233	233
Sulfate (Smith-Dorsey)	233	233
Sulfate (Upjohn)	247	247
Sulfate, Racemic	233	233
Epinephrine	236	236
(Wilson)	236	236
Hydrochloride 1:1,000 (Abbott)	237	237
Hydrochloride 1:1,000 (Barry)	237	237
Hydrochloride 1:1,000 (Brewer)	237	237
Hydrochloride 1:1,000 (Bristol)	237	237
Hydrochloride 1:1,000 (Endo)	237	237
Hydrochloride 1:1,000 (Lakeside)	237	237
Hydrochloride 1:1,000 (Lederle)	238	238
Hydrochloride 1:1,000 (Upjohn)	238	238
Hydrochloride 1:1,000 (U. S. Standard Prod.)		

	PAGE
Epinephrine—(Continued)	
Hydrochloride 1:1 000 (Warren Teed)	238
Hydrochloride 1:1 000 (Wilson)	238
Hydrochloride 1:100 (Bristol)	240
Hydrochloride 1:100 (Burroughs Wellcome)	240
Hydrochloride Solution	240
in Oil Suspension	612
in Oil Suspension 1:500	238
in Oil 1:500 (Abbott)	239
in Oil 1:500 (Endo)	239
in Oil 1:500 (Lakeside)	239
in Oil 1:500 (P-D & Co.)	239
in Oil 1:500 (Smith Dorsey)	239
Solution	236
Epival Soluble (Winthrop Stearns)	461
Ergosterol in Oil Irradiated	564
Ergot Asept c	430
(P D & Co.)	431
Ergotamine Tartrate	431
Erythr-yl Tetranitrate (Burroughs Wellcome)	273
Tetranitrate (Merck)	273
Erythrol Tetranitrate Tablets	272
Estinyl (Schering)	380
Estriol	365 613
(Abbott)	366
(Lilly)	366
Estrogenic Hormones (Barry)	368
Substances (Ayerst McKenna & Harrison)	368
Substances (Barry)	368
Substances (B organic)	368
Substances (Breon)	369
Substances (Bristol)	369
Substances (Cole)	369
Substances (Forbes)	369
Substances (Lakeside)	370
Substances (Lecolin)	370
Substances (Viller)	370
Substances (Reed & Carnrick)	370
Substances (S & D)	371
Substances (Smith Dorsey)	371
Substances (Water Insoluble)	367
Substances (Water Soluble)	372
Petrogenic (Lakeside)	370
Natural	365
Synthetic	373
Estromone (Endo)	369
Estrone	366
(Abbott)	367
(Lilly)	367
Estronat (National Drug)	370
Estrovarin (Warren Teed)	372
Estrugenone (Premiers Urban)	369
Estrusol (Carroll Dunham Smith)	371
Est-nyl Estradiol	379 614
Ethyl Aminobenzoate	47
Chloride	38
Ethylene	38
(Liquid Carbonic Corp.)	39
(Puritan Compressed Gas Corp.)	39
Gas Medical (Ohio Chemical)	39
Ethylstibamine	171 614
Eucatropone Hydrochloride	257
Hydrochloride (Werner)	257
Euphthalmine Hydrochloride (Schering & Glaxo)	257
Euquinine (Merck)	169
Euresol pro Capillis (B Thuber-Knoll)	124
Extrala (Lilly)	357

	PAGE
Fatty Acids and Iodized Fats	422
Ferric Ammonium Citrate	351
Ferrous Lactate	616
Fibrin Ferments and Thromboplastic Substances	352
Fibrin Foam	435, 616
Foam and Thrombin (Human) (Cutler)	435
Fluorescein (Merck)	293
Sodium	292
Folic Acid	537, 559, 617
Acid (Abbott)	559
Acid (American Pharm.)	559
Acid (Kremers-Urban)	559
Acid (Strassenburgh)	559
Acid Preparations	559
Follutein (Squibb)	405
Folvite (Lederle)	559
Food, Epidermal and Incidental Allergens (Arlington) ..	2
Epidermal and Other Extracts	2
Formaldehyde	88
(Merck)	89
Solution	89
Formalin	89
Fuadin (Winthrop-Stearns)	175
Fungicides	119
Fungus Allergens (Arlington)	9
Extracts	9
Extracts (Abbott)	9
Furacin (Eaton)	91
Furan Derivatives	89
Furunculosis Vaccine (P. D. & Co) ..	510
G	479
.....	480
.....	481
.....	479
.....	480
.....	480
.....	480
.....	481
.....	481
.....	481
.....	481
.....	342, 618
.....	343
.....	343
.....	343
.....	333
.....	435
.....	436
.....	575
Gelatin Sponge, Absorbable	434
Gelfoam (Upjohn)	87
Gentian Violet	88
Violet (Coleman & Bell)	88
Violet (National Aniline)	269, 619
Gitalin (Amorphous)	270
(Amorphous) (Rare)	386
Globin Insulin with Zinc	387
Insulin with Zinc (Burroughs Wellcome)	387
Insulin with Zinc (Squibb)	330
Glucophylline (Abbott)	509
Glycerinated Vaccine Virus	341
Glycotauro (H. W. & D)	332
Glynazan (First Texas)	332
Glytheonate (Patch)	523
Cold Compounds	525, 619
Sodium Thiomalate	525
and Sodium Thiosulfate	

	PAGE
Gold Compounds—(Continued)	
Sodium Thiosulfate (Abbott)	526
Sodium Thiosulfate (Merck)	526
Sodium Thiosulfate (Searle)	526
Gonadotropic Substances	491
G Strophanthin	370
Guanafol Hydrochloride (Lilly)	164
Gynergen (Sandoz)	431
Halazone	94
(Abbott)	95
Halibut Liver Oil with Viosterol	568
Liver Oil with Viosterol (International Vitamin)	569
Liver Oil with Viosterol (McKesson & Robbins)	569
Haliver Oil with Viosterol (Abbott)	569
Oil with Viosterol (P D & Co)	569
Halogen Compounds	91
Heavy Liquid Petrolatum	344
Hemetics	347
Hemo Pak (Johnson & Johnson)	437
Heparin Sodium	348, 620
Sodium (Abbott)	349
Sodium (Upjohn)	349
Hexabione Hydrochloride (Merck)	558
Hexamethylenamine	128
Hexamethylenetetramine	128
tetraiodide	423
Hexavitamin	573
(Merrell)	574
(Walker)	574
Hexestrol	380, 620
(Massengill)	381
(Merrell)	381
Hexethal Sodium	459 621
Hexobarbital Soluble	460 622
Hippuran	300 623
(Mallinckrodt)	301
Histamine-Antagonizing Agents	21
Holocaine (Manhattan Eye)	57
Hydrochloride (Winthrop Stearns)	57
Homatropine Hydrochloride	258, 634
Hydrochloride (Merck)	258
Methylbromide	258
Hormones and Synthetic Substitutes	359
Human Convalescent Measles Serum (Samuel Deutsch)	486
Convalescent Scarlet Fever Serum (Samuel Deutsch)	486
Immune Globulin	473
Measles Immune Serum	485
Plasma, Citrated Normal	474
Scarlet Fever Immune Serum	496
Serum Albumin Normal	476
Serum Immune Globulin	474, 487
Serum Normal	475
Hyclorite (Pa. Salt Co.)	95
Hydodan Bitartrate (Endo)	28
Hydantoin Derivatives	443
Hykinone (Abbott)	573
Hypnotics and Sedatives	440
Iletin (Lilly)	390
Immune Globulin Human	473
Globulin, Human Serum	474
Serum Globulin (Human) (Cutler)	474, 487
Serum Globulin (Human) (Lederle)	474
Serum Globulin (Human) (S & D)	474
Serum Globulin (Human) (Wyeth)	474
Serum (Human), Measles	485
Serums for Prophylactic or Therapeutic Purposes	477
Immunity Tests Toxins for	513

	PAGE
Influenza Virus Vaccine, Types A and B	489
Virus Vaccine, Types A and B (Lilly)	489
Virus Vaccine, Types A and B (National Drug)	490
Virus Vaccine, Types A and B (Pitman-Moore)	490
Virus Vaccine, Types A and B (S. & D.)	490
Virus Vaccine, Types A and B (Squibb)	490
Insulin	387
(S. & D.)	390
(Squibb)	390
Hydrochloride	387
Injection	387
Injection-Protamine Zinc	391
Labeling Regulations	385
Preparations	386
Zinc, Crystalline Injection	393
Zinc, Crystals	393
with Zinc, Globin	386
Intocostin (Squibb)	211
Intracutaneous Tuberculin for the Mantoux Test (Lederle)	520
Invert Sugar Solution	217, 624
Iocamfen	96, 625
(Schering & Glatz)	96
Iodeikon (Mallinckrodt)	310
Iodinated Castor Oil	523, 625
Iodine Compounds	201
Compounds for Roentgenography, Water-Soluble	299
Compounds for Systemic Use	421
Dusting Powders	96
and Iodine Derivatives	96
Preparations Containing Free Iodine	96
Iodized Fats and Fatty Acids	422
Oil	298, 424
Iodoalphonic Acid	301, 625
Iodobismutol with Benzocaine (Squibb)	198
Iodobismuthite Sodium	197, 625
Iodobismuthite Sodium with Ethyl Aminobenzoate	198, 627
Iodobrassid	298, 423, 627
Iodochlorohydroxyquinoline	202
Iodophthalein Sodium	309
(Merck)	310
Iodopyracet Compound Solution	302, 627
Concentrated Solution	303
Injection	303
Iodopyracet Concentrated Solution	629
Ipral Sodium (Squibb)	466
Iron and Iron Compounds	350
Lactate	351
Salts, Complex	351
Salts, Simple	351
Isoamylethylbarbiturate Sodium	452
Isoamylethylmalonylurea	451
Isobornyl Thiocyanacetate-Technical	119, 629
Iso Iodeikon (Mallinckrodt)	314
Isonipeaine	31
Iso-Par Coparaffinate (Medical Chemicals)	98
Isoaraffinic Acids	97
Jennerian Vaccine	509
Kayquinone (Abbott)	571
Kelene (Merck)	38
Kephalin, Impure	352
Kinney's Yeast Extract (Kinney & Co.)	548
Koromex Cream (Holland-Rantos)	287
Jelly (Holland-Rantos)	287
Vaginal Applicator (Holland-Rantos)	288
Korotrin (Winthrop-Stearns)	405
Krondremul (Patch)	344

	PAGE
Lac Bismo (Hart)	343
Lactamin (Wyeth)	415
Lactikol Applicator (Durex)	286
Cream (Durex)	286
Jelly (Durex)	286
Lactohavin	553
Laxatives	343
Leisgallol (Bilhuber Knoll)	216
Lipodol (Fougera)	424
40% Iodine (Fougera)	299
Radiologique Ascendant	299, 629
Radiologique Ascendant (Fougera)	299
Lipo-Adrenal Cortex	361
Cortex (Upjohn)	362
Lipiodine (Ciba)	299, 474
Lipotropic Agents	475
Liquid Paraffin	344
Petrolatum Emulsion	344
Petrolatum Emulsion (Smith Dorsey)	344
Petrolatum Heavy	344
Liver and Stomach Preparations	354
Liver Stomach Concentrate	355
Lorophyn Jelly (Eaton)	287
Jelly Applicator (Eaton)	287
Suppositories (Vaginal) (Eaton)	290
Luminal (Winthrop Stearns)	463
Sodium (Winthrop-Stearns)	465
Lunosol (Hille)	115
Lygel Vaginal Appl. cator (Special Formula Corp.)	288
Vaginal Cream (Special Formula Corp.)	288
Vaginal Jelly (Special Formula Corp.)	288
Lygenes Vaginal Suppositories (Special Formula Corp.)	291
Mandelic Acid	127
Acid (Gane & Ingram)	127
Acid (Mallinckrodt)	127
Acid (Merck)	127
Acid Derivatives	127
Acid Racemic	127
Mannitol	293, 630
(S & D)	294
Hexanitate	273, 630
Hexanitate (Breon)	274
Hexanitate (Cole)	275
Hexanitate (Flint Eaton)	275
Hexanitate (National Drug)	275
Hexanitate (Rorer)	275
Hexanitate (Smith Dorsey)	275
Hexanitate (Squibb)	275
Nitrate (Abbott)	274
Mapharsen (P. D. & Co.)	183
Measles Convalescent Serum	485
Human Convalescent Serum (Samuel Deutsch)	486
Immune Serum Human	485
Immune Serum (Human) (Milwaukee Serum Center)	486
Prophylactic	478
Mecholyl Brom de (Merck)	252
Chloride (Merck)	254
Medinal (Schering & Glatz)	455
Menadione	571
(Breon)	571
(Dwight)	571
(Endo)	571
(Lakes de)	571
(McNeil)	572
(Merck)	572
(S & D)	572
(U. S. Vitamin Corp.)	572

Menadione—(Continued)		PAGE
(Vale)		572
Bisulfite		572
Sodium Bisulfite		572
Sodium Bisulfite (Merrell)		573
Meonine (Wyeth)		416
Meperidine Hydrochloride		31, 631
Meprane Dipropionate (Reed & Carnrick)		383
Meralluride Sodium Solution		316, 632
Merbromin		102
(Premo)		103
Mercocresols		104, 632
Mercresin (Upjohn)		105
Mercurhydrin Sodium (Lakeside)		317
Mercuric Cyanide		100
Cyanide (Mallinckrodt)		100
Cyanide (Merck)		100
Oxide, Yellow		101
Potassium Iodide		101, 633
Mercurochrome (H W & D.)		103
Mercurophylline Injection		317
Mercury Metal Compounds		100
Compounds		316
Inorganic Metal Compounds		100
Organic Metal Compounds		102
Mercuzanthin (Campbell)		319
Merphenyl Borate (Hamilton)		109
Nitrate (Basic) (Hamilton)		110
Merthiolate		105, 634
(Lilly)		105
Sodium		105
Mersalyl and Theophylline		319
and Theophylline Injection		320
Mesopin (Endo)		259
Mestibol		381, 634
Mestibol		410
"		98
"		346
"		107
"		251, 635
"		252
Carotide		30
Methadon		30, 636
Methadone Hydrochloride		31
Hydrochloride (Abbott)		31
Hydrochloride (Massengill)		227, 636
Methamphetamine Hydrochloride		24, 638
Methapyrilene Hydrochloride		128
Methenamine		128
(Abbott)		128
(Merck)		128
(Merrell)		128
(Miller)		128
Compounds		422, 639
Tetraiodide		306, 639
Methiodal Sodium		415, 640
Methionine		87
Methyl Violet		87
Methylrosaniline Chloride		406
Methyltestosterone		407
(Rare)		278, 641
Metrazol		279
(Bilhuber-Knoll)		54
Metycaine Hydrochloride (Lilly)		345
Mineral Oil (Smith Oil & Refining)		345
Oil (Squibb)		344
Oil, White		573
Mixed Vitamin Preparations		56
Monocaine Hydrochloride (Novocol)		382
Monomestrol (Wallace & Tiernan)		

	PAGE
Mucin-Aluminum Hydroxide Magnesium Trisilicate	337, 641
Mucotin (Harrower)	338
Mydriatics Synthetic	256
Myochrysine (Merck)	525
Naphazoline Hydrochloride	241, 642
Naphuride Sodium (Winthrop Stearns)	204
Naturally Produced Antibodies	485
Neocarsphenamine	181
(Abbott)	182
(Merck)	182
(Squibb)	182
Neohetramine Hydrochloride (Wyeth)	24
Neo-Iopax (Schering)	308
Neonal (Abbott)	457
Neosalvarsan (Winthrop-Stearns)	182
Neo-Solvol (P D & Co)	116
Nicotinyl Stibamine Glucoside (Burroughs Wellcome)	174
Neostibosan (Winthrop Stearns)	173
Neostigmine	254
Bromide	254
Methylsulfate	255
Neo-Synephrine Hydrochloride (Winthrop Stearns)	243
Nervous System Stimulants Central	278
New Tuberculin, B E	520
Tuberculin B E, Dried	521
Tuberculin T R	521
Tuberculin T R Dried	521
Niacin	555
(Merck)	555
(U S Vitamin Corp)	556
(Warren Teed)	556
Niacinamide	556
(Brewer)	556
(Cole)	557
(Harrower)	557
(Merck)	557
(Miller)	557
(U S Vitamin Corp)	557
(Walker Vitamin)	557
Nicotinamide	556
(Abbott)	556
(American Pharm)	556
(Burroughs Wellcome)	557
(Drug Products)	557
(Endo)	557
(Flint Eaton)	557
(Lakeide)	557
(Merrell)	557
(Vale)	557
(Warren Teed)	557
and Nicotinic Acid	555
and Nicotinic Acid Preparations	555
Nicotinic Acid	555
Acid (Abbott)	555
Acid (American Pharm)	555
Acid (Endo)	555
Acid (Flint Eaton)	555
Acid (International Vitamin)	555
Acid (Merrell)	555
Acid (National Drug)	556
Acid (P D & Co)	556
Acid (Putman Moore)	556
Acid (Smith Dorsey)	556
Acid (Upjohn)	556
Acid (Walker Vitamin)	556
Acid Amide	556

Nicotinic Acid—(Continued)		PAGE
Acid Amide (International Vitamin)	557	557
Acid Amide (Upjohn)	557	557
Acid and Nicotinamide		
Acid and Nicotinamide		
Nikethamide		
(Abbott)	281	281
(Breon)	281	281
(Burlington's)	281	281
(Drug Products)	281	281
(Endo)	281	281
(Flint, Eaton)	281	281
(National Drug)	281	281
(Premo)	281	281
(Carroll Dunham Smith)	281	281
(Smith-Dorsey)	281	281
(Upjohn)	281	281
(Warner)	281	281
Nitrates, Organic	272	272
Nitrofurazone	89, 644	89, 644
Nitromersol	106	106
Normal Human Plasma (Cutter)		475
Human Plasma (Samuel Deutsch)	475	475
Human Plasma (Hyland)	475	475
Human Serum	475	475
(Samuel Deutsch)	476	476
Human Serum Albumin	476	476
Human Serum Albumin (Cutter)	476	476
Norodin Hydrochloride (Endo)	228	228
North American Anti-Snake Bite Serum	477	477
Novatrin (Campbell)	258	258
Novocain (Winthrop-Stearns)	62	62
Nupercaine Hydrochloride (Ciba)	52	52
Octofollin	584	584
Oils, Iodized	297, 424	297, 424
Old Tuberculin	519	519
Tuberculin, Human Strain Concentrated (Lilly)	520	520
Oleo-Blend Vitamin A (White)	546	546
Oleo Vitamin A (Abbott)	546	546
	546	546
	546	546
	545	545
	546	546
A and D, Concentrated	566	566
A and D, Concentrated (McKesson & Robbins)	566	566
Oleum Percomorphum (Flint, Eaton)	570	570
Percomorphum (Mead Johnson)	570	570
Opium Principles and Derivatives	27	27
Oridine	424, 644	424, 644
(Lilly)	424	424
Ortal Sodium (P. D. & Co.)	460	460
Ortho Vaginal Applicator (Ortho)	289	289
Ortho-Creme (Ortho Pharm.)	288	288
Orthoform	48, 645	48, 645
(Winthrop-Stearns)	48	48
Orthoform-New	48	48
Ortho-Gynol Vaginal Jelly (Ortho Pharm.)	289	289
Ouabain	270	270
(Merck)	271	271
(Carroll Dunham Smith)	270	270
Ovaries	362	362
Oxazolidine Derivatives	444	444
Ox Bile Extract	340	340
Oxidized Cellulose	436, 645	436, 645
Oxophenarsine Hydrochloride	182	182
Oxyquinoline Benzoate	646	646
Oxytocics	437	437

	PAGE
Pancreas	383
Papaverine	213, 647
Para Aminohippuric Acid	294, 648
(S & D)	295
Paraffin Pliable	437
Parasympathomimetic Agents	249
Parathyroid	394
Extract	395
Extract (Lilly)	395
Injection	395
Solution	395
Parenammine (Winthrop-Stearns)	415
Parenteral Solutions	432
Parosidin (P. D. & Co.)	356
Parresined Lace Mesh (Abbott)	438
Pasteur Antirabic Vaccine	391
Pediculicides	119
Penicillin	148
Calcium (Abbott)	158
Calcium (Bristol)	151, 156
Calcium (Commercial Solvents)	151
Calcium (Heyden)	151
Calcium (Merck)	152
Calcium (Pfizer)	152
Calcium (Premo)	157, 158
Calcium (Schenley)	152, 157, 158
Calcium (Squibb)	159
Calcium (Upjohn)	159
Calcium (Winthrop-Stearns)	159
Calcium (Wyeth)	153
Calcium in Oil and Wax (Abbott)	154
Calcium in Oil and Wax (Bio-Ramo)	154
Calcium in Oil and Wax (Bristol)	154
Calcium in Oil and Wax (Sterone)	156
Inhalation Therapy	158
G Potassium (Abbott)	151, 156, 158
G Potassium (Commercial Solvents)	151, 157, 158
G Potassium (Dwight)	151
G Potassium (Lilly)	152, 156, 158
G Potassium (Pfizer)	152
G Potassium (Premo)	156
G Potassium (Schenley)	152
G Potassium (Upjohn)	156, 159
G Potassium in Oil and Wax (Commercial Solvents)	154
G Potassium in Oil and Wax (Lilly)	155
G Potassium in Oil and Wax (Premo)	155
G Procaine (Pfizer)	153
G Procaine in Oil (Abbott)	154
G Procaine in Oil (Commercial Solvents)	155
G Procaine in Oil (Mertell)	155
G Procaine in Oil (Pfizer)	155
G Procaine in Oil (Premo)	153
G Procaine in Oil (Squibb)	153
G Sodium (Bio-Ramo)	151
G Sodium (Commercial Solvents)	151
G Sodium (Lederle)	151
G Sodium (Lilly)	152
G Sodium (Merck)	152
G Sodium (Pfizer)	152
G Sodium (Premo)	152, 154
G Sodium (Squibb)	152, 157
G Sodium (Upjohn)	153
G Sodium in Oil and Wax (Bio-Ramo)	154
G Sodium in Oil and Wax (Mertell)	155
G Sodium in Oil and Wax (Premo)	155
Oral Administration	156
Parental Use in Aqueous Solution	150
Parental Use for Prolonged Action	153

Penicillin—(Continued)		PAGE
Sodium (Abbott)	151	151
Sodium (Bio Ramo)	151	151
Sodium (Bristol)	151	151
Sodium (Burroughs Wellcome)	151	151
Sodium (Commercial Solvents)	151	151
Sodium (Heyden)	151	151
Sodium (Lederle)	151	151
Sodium (Lilly)	152	152
Sodium (Merek)	152	152
Sodium (Merrell)	152	152
Sodium (P. D. & Co.)	152	152
Sodium (Pfizer)	152	152
Sodium (Schenley)	152	152
Sodium (Warner)	153	153
Sodium (Winthrop-Stearns)	153	153
Sodium (Wyeth)	153	153
Topical Application	158	158
Pentamethylenetetrazol	278, 641	278, 641
Pentavalent Gas Gangrene Antitoxin	480	480
Pentobarbital Sodium	461	461
Sodium (Lakeside)	461	461
Sodium (Lilly)	462	462
Sodium (Premo)	462	462
Soluble	461	461
Pentothal Sodium (Abbott)	468	468
Percomorph Liver Oil	569, 649	569, 649
Pernoston (Ames)	457	457
Pernox Vaginal Capsules (Pernox)	291	291
Peroxide Sodium	121	121
Zinc, Medicinal	121	121
Peroxides	120	120
Petrobran (Sargent's Drug Store)	345	345
Pertussis Endotoxoid-Vaccine	507	507
Immune Serum (Human)	487	487
Immune Serum (Human) (Hyland)	487	487
Immune Serum (Human) (Philadelphia Serum Exchange)	438	438
Vaccine	505	505
Vaccine (Cutter)	505	505
Vaccine (National Drug)	506	506
Vaccine (P. D. & Co.)	506	506
Vaccine (S & D.)	506	506
Vaccine (Squibb)	506	506
Vaccine (Upjohn)	506	506
Vaccine (Wyeth)	506	506
Vaccine Alum Precipitated	506	506
Vaccine, Alum Precipitated (P. & D. Co.)	507	507
Vaccine and Antitoxin, Combined	507	507
Tetanus Toxoids	508	508
Im Precipitated (Upjohn)	508	508
Petrolatum	345	345
Liquid Emulsion	344	344
Liquid, Heavy	344	344
Phanodorn (Winthrop-Stearns)	458	458
Pharmaceutic and Therapeutic Aids	434	434
Phemerol Chloride (P. D. & Co.)	77	77
Phenacaine Hydrochloride	56	56
Hydrochloride (Werner)	57	57
Phenarsone Sulfoxylate	187, 649	187, 649
Phenobarbital	462	462
(Abbott)	462	462
(American Pharm)	463	463
(Breon)	463	463
(Buffington's)	463	463
(Flint, Eaton)	463	463
(Gane & Ingram)	463	463

	PAGE
Phenobarbital—(Continued)	
(Harrower)	463
(Merck)	463
(Merrell)	463
(Miller)	463
(Smith Dorsey)	463
(Upjohn)	463
(Vale)	463
(Warren Teed)	463
Sodium	463
Sodium (Abbott)	464
Sodium (Endo)	464
Sodium (Gane & Ingram)	464
Sodium (Mallinckrodt)	464
Sodium (Merck)	464
Sodium (Merrell)	464
Sodium (Warren Teed)	465
Soluble	464
Phenobarbitone	462
Soluble	464
Phenolphthalein Dyes	308
Phenolsulfonphthalein	310
(H W & D)	311
(National Aniline)	312
Phenoltetrachlorophthalein	312, 631
Phentetotrialein Sodium	312, 651
Phenylcarbinol	49
Phenylephrine Hydrochloride	242, 651
Phenylethylmalonylurea	462
Phenylmercuric Borate Tincture	103, 652
Phenylmercuric Compounds	107
Nitrate	109
Nitrate Basic	109
Picrate Tincture	110, 653
Picrate Tincture (Hamilton)	111
Phenylpropanolamine Hydrochloride	244, 654
Phenylpropylmethylamine	246, 654
Phosphaljel (Wyeth)	315
Phthalysulfathiazole	132, 655
Pieragol (Wyeth)	119
Picrotoxin	281
(Abbott)	281
Piperocaine Hydrochloride	54, 656
Pitocin (P D & Co)	398
Pitresmin (P D & Co)	399
Tannate (P D & Co)	399
Pisutarg	396
Pituitrin (P D & Co)	401
Placenta	401
Placental Extract	473
Plague Vaccine	509
Vaccine (Cutter)	509
Plestrin (Forbes)	369
Pliable Paraffin	437
Poison Ivy Extract	17
Ivy Extract (Abbott)	17
Ivy Extract (Hollister Suer)	17
Ivy Extract (Lederle)	18
Ivy Extract (P D & Co)	18
Ivy Extract (Pitman Moore)	18
Oak Extract	19
Oak Extract (Hollister Suer)	19
Oak Extract (Lederle)	20
Oak Extract (Pitman Moore)	18, 19
Sumach Extract (Pitman Moore)	20
Pollen Allergens (Arlington)	31
Extracts	10
Extracts (Abbott)	10

Riboflavin—(Continued)		PAGE
(Endo)	554
(Harrower)	554
(International Vitamin)	554
(Merck)	554
(Merrell)	554
(Premo)	554
(U. S. Vitamin Corp.)	554
(Upjohn)	554
(Walker)	555
(Warren-Teed)	555
Preparations	555
Riodine (Gallia)	423
Rocky Mountain Spotted Fever Vaccine	510
Mountain Spotted Fever Vaccine (Squibb)	511
Salicylic Acid	423
Salicylic Acid (Squibb)	34
Salicylic Acid (Squibb)	320
Salicylic Acid (Squibb)	451
Salicylic Acid (Squibb)	122
Scarlet Fever Antitoxin	483
Fever Convalescent Serum	486
Scarlet Fever Antitoxin	486
Fever Convalescent Serum	486
Scarlet Fever Antitoxin	516
Fever Convalescent Serum	483
Scarlet Fever Antitoxin	483
Fever Convalescent Serum	493
Scarlet Fever Antitoxin	493
Fever Convalescent Serum	494
Scarlet Fever Antitoxin	494
Fever Convalescent Serum	494
Scarlet Fever Antitoxin	515
Fever Convalescent Serum	515
Scarlet Fever Antitoxin	515
Fever Convalescent Serum	515
Scarlet Fever Antitoxin	515
Fever Convalescent Serum	516
Scarlet Fever Antitoxin	516
Fever Convalescent Serum	494
Scarlet Fever Antitoxin	495
Fever Convalescent Serum	80
Red	80
Red (Heilkraft)	80
Red (Merck)	80
Red (National Aniline)	80
Red (P. D. & Co.)	81
Red, Biebrich	80
Red, Medicinal	80
Red Sulfonate	81, 666
Red Sulfonate (National Aniline)	81
Scillaren	271, 666
(Sandoz)	272
Scillaren-B	272, 668
(Sandoz)	272
Sclerosing Agents	216
Agents, Astringents and Caustics	214
Scopolamine Hydrobromide	259
Hydrobromide (Merck)	259, 668
Stable	259
Stable (Hoffmann-LaRoche)	455, 669
/Secal Sodium	467
(Lilly)	440
Sedatives and Hypnotics	472
Serum(s)	476
Albumin, Normal Human	434
Antibacterial	434

Serum(s)—(Continued)	PAGE
Antitoxic	477
Immune Globulin Human	474
Immune for Prophylactic or Therapeutic Purposes	477
Normal Human	475
Normal or Normal Blood Derivatives	472
and Vaccines	469
Shark Liver Oil	570, 670
Silver	111
Chloride, Colloidal	115
Iodide, Colloidal	111
Nitrate	117
Nitrate (Abbott)	118
Nitrate (Aristol)	118
Nitrate (S & D)	118
Picrate	118, 670
Preparations Colloidal	111
Protein, Mild	116
Protein, Strong	117
Protein, Strong (Merck)	117
Salts	117
Trinitrophenolate Monohydrate	118
Silvol (P. D. & Co.)	117
Sodium (Lisman Moore)	423
Skiabart (Merck)	297
Skiolan (Winthrop-Stearns)	307
Smallpox Vaccine	509
Sobiaminol Mass	199, 671
(Lilly)	199
Sodium Ascorbate (Barry)	563
Ascorbate (Breon)	563
Ascorbate (Central Pharmacal)	563
Ascorbate (Endo)	563
Ascorbate (Kremers Urban)	563
Ascorbate (Lincoln)	563
Ascorbate (Merrill)	563
Ascorbate (Rorer)	563
Ascorbate Injection	562
Benzoate	295
(Breon)	296
Butabarbital	456
Butisol (McNeil)	456
Dehydrocholate	341, 673
Dehydrocholate (Breon)	341
Dehydrocholate (Endo)	342
Dehydrocholate (Carroll Dunham Smith)	342
Diethylbarbiturate	455
Diethylmalonylurea	455
Ethylmercurithiosalicylate	105, 634
Folate	559, 673
Folate (Kremers Urban)	560
Folvite (Lederle)	560
Hexethal	459
Hypochlorite Solution	95, 673
Iodomethamate	307, 674
Isoamylethylbarbiturate	452
Lactate	432
Lactate Injection	432
Morrhuate (Breon)	218
Morrhuate (Endo)	218
Morrhuate (Lakeside)	218
Morrhuate (National Drug)	219
Morrhuate (Searle)	219
Morrhuate (Winter)	219
Morrhuate (Upjohn)	219
Morrhuate Injection	218
PABA (International Vitamin)	205
PABA (Wyeth)	205
Para Aminobenzoate	204, 674

Sodium Ascorbate—(Continued)		PAGE
Para-Aminohippurate (S. & D.)	295
Pentobarbital	461
Peroxide	121, 675
Peroxide (Merck)	121
Probarbital	466
Pteroylglutamate	559
Ricinoleate Solution	219, 675
Seconal	455
Sotradecol (Wallace & Tiernan)	221
Sulfadiazine	145
Sulfadiazine (Lederle)	146
Sulfadiazine (S. & D.)	146
Sulfadiazine (Squibb)	146
Sulfamerazine	146
Sulfapyrazine	147
Tetradecyl Sulfate	220, 676
Thiopental	467
Vinbarbital	468
Soricin Sclerosing Solution 2% (Merrell)	220
Standards and Tests	575
Staphylococcus Antitoxin	483
Toxoid	500
Toxoid (Lederle)	500
Toxoid (National Drug)	501
Toxoid (P. D. & Co.)	501
Toxoid (Pitman-Moore)	501
Toxoid (S. & D.)	501
Toxoid-Vaccine Mixture	512
Vaccine	510
Vaccine (Lilly)	510
Starch Derivative Dusting Powder	438, 676
Stibamine Glucoside	173, 677
Stibophen	174
Stilbestrol	374
Stilpalmitate	383, 678
(Abbott)	383
Stomach, Dried	357
and Liver Preparations	354
Powdered	357
Stovarsol (Merck)	186
Streptococcus Antitoxin, Scarlet Fever	483
Streptomycin	159
Calcium Chloride Complex (Merck)	162
Calcium Chloride Complex (Merrell)	162
Calcium Chloride Complex (Premo)	163
Hydrochloride (Squibb)	163
Sulfate (Abbott)	162
Sulfate (Pfizer)	163
Sulfate (Premo)	163
Sulfate (Upjohn)	163
Succinylchloramide	95
(National Aniline)	96
Succinylsulfathiazole	133
Sudan IV	80
Sugar Solution, Invert	217
Sulfadiazine	134
(Abbott)	136
(American Pharm.)	136
(Buffington's)	136
(Cole)	136
(Flint, Eaton)	136
(Harrower)	136
(Lederle)	136
(Lilly)	136
(McNeil)	136
(Merrell)	137
(Miller)	137
(P. D. & Co.)	137

	PAGE
<i>Sulfadiazine—(Continued)</i>	
(Litman Moore)	137
(Rorer)	137
(S & D)	137
(Carroll Dunham Smith)	137
(Smith Dorsey)	137
(Squibb)	137
(Upjohn)	137
(Vale)	137
(Winthrop-Stearns)	137
Sodium	145
Sodium (Abbott)	135
<i>Sulfaguanidine</i>	137
(Lederle)	138
(Squibb)	133
<i>Sulfamerazine</i>	138
(Abbott)	140
(American Pharm.)	140
(Lederle)	140
(Lilly)	140
(Mitsunobu)	140
(P. D. & Co.)	140
(S & D)	140
(Squibb)	140
(Upjohn)	140
Sodium	146
Sodium (Lederle)	147
Sodium (S & D)	147
<i>Sulfamethyliazine</i>	138
<i>Sulfanilamide</i>	140
(Abbott)	142
(American Pharm.)	142
(Ciba)	142
(Drug Products)	142
(Endo)	142
(Flint Eaton)	142
(Gane & Ingram)	142
(Horton & Converse)	142
(Lederle)	142
(Malibac)	142
(Merck)	142
(Merrill)	142
(Miller)	142
(National Drug)	142
(P. D. & Co.)	142
(Pitman Moore)	142
(Schieffelin)	142
(S & D)	142
(Carroll Dunham Smith)	142
(Upjohn)	142
(Watren Teed)	142
2 Sulfanilamidopyrimidine	134
2 Sulfanilyl Aminopyrimidine	134
Sulfanilylguanidine monohydrate	137
<i>Sulfapyrazine</i>	143, 679
(Mead Johnson)	144
Sodium	147, 680
Sodium (Mead Johnson)	148
<i>Sulfarephenamine</i>	183
(Abbott)	184
(Merck)	184
B Smith	179
<i>Sulfasuxidine (S & D)</i>	133
<i>Sulfathalidine (S & D)</i>	133
Sulfobromophthalein Sodium	314
Sulfonchrylate Preparations and Substitutes	124
Sulfonal	447
<i>Sulfonamide Compounds</i>	129
Sodium Salts	144

	PAGE
p-Sulfonedichloramidobenzoic Acid	94
Sulfonethylmethane	446
Sulfonmethane	447
Sulfonmethanes	446
Suprarenalin (Armour)	235
1:100 (Armour)	240
1:1,000 (Armour)	237
Suprarenin Bitartrate (Winthrop-Stearns)	236
Suramin Sodium	203
Sympatholytic Agents	248
Sympathomimetic Agents	223
Synophylate (Central Pharmacal)	331
Synthetic Mydriatics	256
Oleovitamin D	563
Syntropan (Hoffmann-LaRoche)	257
Testes	405
Testosterone Propionate	407
Propionate (Rare)	408
Tests and Standards	575
Tetanus Antitoxin	484
Antitoxin, Concentrated	484
Antitoxin, Refined	484
and Gas Gangrene Antitoxins	481
-Gas Gangrene Antitoxin (Cutter)	482
-Gas Gangrene Antitoxin (Lederle)	482
-Gas Gangrene Antitoxin (Lilly)	482
-Gas Gangrene Antitoxin (National Drug)	482
-Gas Gangrene Antitoxin (P. D. & Co)	482
-Gas Gangrene Antitoxin (Pitman-Moore)	482
-Gas Gangrene Antitoxin (Squibb)	482
-Gas Gangrene Antitoxin (U. S. Standard Prod.)	482
-Gas Gangrene Antitoxin (Wyeth)	474
Toxoid	501
Toxoid (Cutter)	501
Toxoid (Lederle)	501
Toxoid, Alum Precipitated	502
Toxoid, Alum Precipitated (Lederle)	502
Toxoid, Alum Precipitated (Lilly)	502
Toxoid, Alum Precipitated (National Drug)	502
Toxoid, Alum Precipitated (P. D. & Co)	503
Toxoid, Alum Precipitated (Pitman-Moore)	503
Toxoid, Alum Precipitated (S & D)	503
Toxoid, Alum Precipitated (Squibb)	503
Toxoid, Alum Precipitated (Wyeth)	503
Toxoid and Bacterial Vaccine Made from <i>H. Pertussis</i> Combined (Cutter)	509
Tetracaine Hydrochloride	64
Tetrachloroethylene	206
Tetraiodophenolphthalein Sodium (Eastman Kodak)	310
Theelin	366
(P. D. & Co)	367
Theelol	365
(P. D. & Co.)	366
Thenylene Hydrochloride (Abbott)	24
Theocin (Winthrop-Stearns)	328
Soluble (Winthrop-Stearns)	329
Theoglycinate (Brayten Pharm.)	331
Theophylline	328
(Merck)	328
(Miller)	329, 681
-Methylglucamine	329
and Sodium Acetate	330, 681
-Sodium Glycinate	322
and Theophylline Compounds	522
Therapeutic Agents, Unclassified	434
and Pharmaceutical Aids	533
Thiamine	

Thiamine—(Continued)

	PAGE
Chloride	549
Hydrochloride	549
Hydrochloride (Abbott)	550
Hydrochloride (American Pharm)	550
Hydrochloride (Ligron)	550
Hydrochloride (Bristol)	550
Hydrochloride (Burroughs Wellcome)	551
Hydrochloride (Cole)	551
Hydrochloride (Drug Prod)	551
Hydrochloride (Dwight)	551
Hydrochloride (Endo)	551
Hydrochloride (Flint, Eaton)	551
Hydrochloride (Harrower)	551
Hydrochloride (Horton & Converse)	551
Hydrochloride (International Vitamin)	551
Hydrochloride (Kremers Urban)	551
Hydrochloride (Lincoln)	551
Hydrochloride (McKesson & Robbins)	551
Hydrochloride (Merck)	552
Hydrochloride (Merrell)	552
Hydrochloride (Miller)	552
Hydrochloride (National Drug)	552
Hydrochloride (Rorer)	552
Hydrochloride (Schiefelin)	552
Hydrochloride (Carroll Dunham Smith)	552
Hydrochloride (Smith Dorsey)	552
Hydrochloride (Squibb)	552
Hydrochloride (U S Vitamin Corp)	552
Hydrochloride (Upjohn)	553
Hydrochloride (Vale)	553
Hydrochloride (Walker Vitamin)	553
Hydrochloride (Warren Teed)	553
Hydrochloride (White)	553
Hydrochloride (Winthrop-Stearns)	552
Hydrochloride (Wyeth)	553
Preparations	549
Thio-Urisol (P D & Co)	195
Thiopental Sodium	467
Thiourea	439, 682
Thonzylamine Hydrochloride	24, 682
Thrombin	354, 683
Topical	354, 683
Topical (P D & Co)	354
Thromboplastin Local (Lederle)	354
Thromboplastin Hess Solution	353
Thyloquinone (Squibb)	572
Thymol Iodide	97
(Merck)	97
Thyroid	408
p-Toluenesulfond chloramide	93
Toxins Bacterial	493
Bacterial, Modified	495
for Immunity Tests	513
Toxin-Antitoxin Mixture	495
Toxoids	496
Triacetyl Pyrogallol	215, 576
Triasyn B	553
B (Premo)	553
Tridromoethanol Solution	40
Trichinella Extract	293
(Lilly)	293
Trichlorbutylidene Glycol	442, 596
Trichloroethylene	41
Tridione (Abbott)	445
Triethanolamine	439
Trimethadione	444, 683
Triphenylamine Hydrochloride	25, 684
Triphenylmethane (Rosaniline) Derivatives	83

	PAGE
Trivalent Gas Gangrene Antitoxin	480
Tryparsamide	189
(Merck)	190
Tuamime	247, 685
(Lilly)	248
Sulfate	248, 685
Sulfate (Lilly)	248
Tuberculin (Pitman-Moore)	518
B. E., New	520
Denys	521
for the Mantoux Test (P. D. & Co.)	520
Old	518
Old (Koch) (P. D. & Co.)	520
Old for the von Pirquet Test (P. D. & Co.)	520
Patch Test (Volmer) (Lederle)	520
Purified Protein Derivative (P. D. & Co.)	518
Tuberculin	516
d-Tubocurarine Chloride	211, 686
(Abbott)	213
(Squibb)	213
Typhoid Vaccine	511
Vaccine (Cutter)	512
Vaccine (Lilly)	512
Vaccine (National Drug)	512
Vaccine (P. D. & Co.)	512
Vaccine (Pitman-Moore)	512
Vaccine (U. S. Standard Prod.)	512
-Vaccine Mixtures	512
Tyrosine	71
(P. D. & Co.)	72
(Penick & Co.)	72
(S. & D.)	72
Unclassified Therapeutic Agents	522
Undecylenic Acid	687
Undulant Fever Vaccine	503
Fever Vaccine (Lederle)	504
Fever Vaccine (National Drug)	504
Fever Vaccine (Pitman-Moore)	504
Unidign (Merrell)	268
Urea	321
(Mallinckrodt)	321
Derivatives	203
Urotropin (Schering & Glatz)	129
Vaccines	438
Bacterial	503
and Serums	469
Vatox Staphylococcus Toxoid-Vaccine (National Drug)	513
Ventriculin (P. D. & Co.)	557
Veronal (Winthrop-Stearns)	455
Vinbarbital Sodium	468, 688
Sodium (S. & D.)	468
Vinethene (Merck)	43
Vinyl Ether	42
Vioform (Ciba)	202
Vioform in Halibut Liver Oil (Mead-Johnson)	569
in Oil	563
in Oil (Abbott)	564
in Oil (American Pharm.)	564
in Oil (International Vitamin)	563
in Oil (McKesson & Robbins)	565
in Oil (Mead Johnson)	565
in Oil (P. D. & Co.)	565
in Oil (Squibb)	489
Viruses, Attenuated Living or Killed	527
Vitamin(s)	531
A	

